









# SAJOUS'S ANALYTIC CYCLOPEDIA OF PRACTICAL MEDICINE

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1946 SUPPLEMENT



PHILADELPHIA

F. A. DAVIS COMPANY, PUBLISHERS

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PRINTED IN THE UNITED STATES OF AMERICA

## PREFACE

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THE END of the War has seen an unusually large number of physicians return from the Armed Forces to civilian practice in a comparatively short time. This situation has presented to the medical profession of this country many serious problems that await solution; not the least of these is the necessity to provide returning physicians with postgraduate training and refresher courses, which they seek so eagerly, in all fields of medicine and surgery. The increased number of residencies and greatly expanded facilities in graduate medical education have thus far failed to meet adequately the unprecedented demands. In this present circumstance the 1946 REVISION SERVICE VOLUME for THE CYCLOPEDIA OF MEDICINE, SURGERY AND SPECIALTIES takes on an added interest and importance. Since it is designed to provide physicians with a convenient, up-to-date, and easily available source of information, it will be found useful to supplement or even, in some cases, to take the place of more formal types of graduate training.

Another problem which confronts the profession of medicine is the importance of disseminating among civilian physicians knowledge of the advances that have been made as the result of wartime medicine and surgery. The lessons learned from the experiences of our Armed Forces must not be laid aside but must be adapted to the needs of peacetime practice. Here again, the 1946 REVISION SERVICE VOLUME serves a useful and timely purpose, because it consists of a group of critical reviews of the progress that has been made in medicine, surgery, and the several specialties during the past year, emphasizing particularly advances that have emanated from the several governmental services.

The Publishers and Editors of this volume are fortunate in having the cooperation of an exceptionally well qualified group of Contributors. Every review, prepared by Authors preeminent in their respective field, represents a well considered, scientific discussion; in each, however, the practical aspects of the subject have not been overlooked. The value and usefulness of this volume is primarily due to the interest and ability of our Contributors, to whom we express our deep appreciation.

In format, the present volume is similar to those of former years, the subject matter being arranged in alphabetical order. Although an effort has been made to include all of the important recent advances in the various fields of medicine, certain subjects that are of special interest have been stressed. Mention should be made of the sections devoted to Anesthesia, Endocrinology, Hematology, and Tropical Medicine. For many years to come, the practitioners of this country will be faced with the necessity of directing and conducting the care of millions of veterans. Because many veterans will require reconditioning, particular attention has been paid

to those subjects which form the basis of an adequate rehabilitation program, namely: Physical Medicine, Occupational Therapy, and Psychotherapy. In addition to a comprehensive review of General Surgery, such subjects as Neurosurgery, Plastic and Reconstructive Surgery, Thoracic Surgery and War Injuries of the Chest have been accorded special consideration. Under the subject of Therapeutics, Streptomycin, Penicillin and Sulfonamide Therapy have been dealt with in great detail.

It is a pleasure for the Editor to announce the return of Dr. Edward L. Bortz, after a prolonged tour of active duty in the United States Navy, to his duties as Assistant Editor, in which capacity he has again been of inestimable service in the preparation of this volume. The sincere thanks of the Editor are also due to Mrs. Jacob Brehm, Jr., and other members of the Editorial Staff, who have been of such help in the preparation of the manuscripts and seeing this volume through the press. The Publishers are to be congratulated upon the appearance of the volume, and are particularly to be commended for their generosity in including two hundred and fifty illustrations, of which two are in color.

It is the sincere hope of all who have been engaged in the preparation of this 1946 REVISION SERVICE VOLUME that it will prove a valuable asset to all the subscribers of THE CYCLOPEDIA OF MEDICINE, SURGERY AND SPECIALTIES, particularly to those who are seeking additional educational opportunities after years of patriotic service to their country.

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# The Cyclopedia of Medicine

Revision Service—1946

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## ALLERGY

MERLE M. MILLER, B.S., M.D., F.A.C.P.

### Histamine and Antihistaminic Substances

**Evaluation of the Histamine Intradermal Test as a General Indicator of Allergy**—While concurring in the belief that allergic manifestations are due to release of histamine, Farmer<sup>1</sup> rejected the inference that allergy is increased sensitivity to this substance. His work failed to confirm Atkinson's suggestion (1941) that allergic and non-allergic individuals can be distinguished by means of an intradermal histamine test.

Using the methods and criteria of the previous study, this investigator tested eighty-six subjects, of whom seventy-six had clinical symptoms of allergy. Sixty-five of these patients had shown positive specific skin test reactions, but, of this number, positive skin reactions to histamine were obtained in only twelve. No positive specific skin reactions were demonstrated by nine patients with nonallergic disorders, but two of them showed positive reactions when tested with histamine.

**Clinical Observations on the Use of Benadryl: a New Antihistaminic Substance**—Work by McElin and Horton<sup>2</sup> has suggested that *benadryl*, a new antihistaminic preparation, is fifteen to thirty times more effective than *amino-*

*phyllin* in relieving bronchial constriction. When compared with *papaverine*, its antagonistic effect on histamine was 650 times greater; on *acetylcholine*, 50 times greater, and on *barium chloride*, 1.3 times greater.

Lethal doses given to albino rats and mice, rabbits, and dogs caused violent excitement, convulsions, and respiratory failure before death. Dogs receiving non-lethal toxic doses showed violent ataxia and excitement, but, apparently, no impairment of vision or mental acuity. No changes were observed in the blood pictures, nonprotein levels, or histopathology of dogs given large but nontoxic amounts of benadryl for an extended period; the marked congestions in the choroid plexuses of these animals are as yet unexplained.

The antihistamine properties of benadryl were tested clinically, using the oral, intravenous (drip method) and, less frequently, the intramuscular routes of administration. The last-named was thought to be somewhat irritating. Gastric analyses were done on seven patients who had multiple sclerosis. In three, intravenous benadryl blocked the rise in the gastric acid curve caused by an injection of histamine; in the fourth case, it was not as great as when histamine was given without a previous injection of benadryl.

This drug was also tested in cold allergy. The patient, whose blood histamine rose during and immediately after exposure to cold, developed a typical wheal and flare when an ice cube was held on his forearm for about three minutes. The test, when repeated on the other arm after an intravenous injection of benadryl, produced a reaction approximately 50 per cent less than the first one.

Symptoms of Ménière's disease and, in one case, accompanying conditions, such as urticaria, hay fever, and allergic headache, were completely relieved by oral benadryl. Marked and at times striking relief was obtained in hay fever (twenty-two cases), in three patients who developed acute urticaria and angioneurotic edema following the use of penicillin and one in which these conditions were observed after the administration of barbiturates, as well as in two cases of recurrent dermatitis and one each of migraine and photophobia with irritation of eyelids due to temperature changes.

In previous work, the authors had obtained only limited and inconsistent results from the use of benadryl in alleviating cephalalgia, but this paper reports three cases in which such attacks, brought on by subcutaneous injections of histamine, were terminated by intravenous injections of benadryl. Such injections failed to bring relief in a case of acute asthma; on the contrary, they seemed to make coughing more difficult and the expectorated material seemed more tenacious.

Benadryl seems to be palliative rather than curative and, in most instances, symptoms recurred when the medication was stopped.

A number of unpleasant side effects occurred, the most frequent being drowsiness, vertigo, dry mouth, and nervousness. In no case were these severe

enough to warrant discontinuation of the therapy.

There were no abnormal changes in the blood counts or urinalyses of a representative group of patients, nor, in a smaller group, were platelet counts or determinations of bleeding time, clotting time, or blood urea nitrogen found to be abnormal.

Results of these preliminary studies seem to warrant further investigation of the effect of benadryl on allergic disorders.

*Benadryl in the Treatment of Urticaria* - O'Leary and Barber<sup>3</sup> reported prompt relief from benadryl in nine out of fifteen patients with acute urticaria, and improvement in five. Only one patient failed to benefit. Benadryl was also given to thirty-five patients with chronic urticaria, accompanied in twenty four cases by angioneurotic edema. Complete disappearance of the lesions, except for a few nonpruritic hives, was attained in twenty-five cases, and in seven fewer lesions and less pruritis were observed. Three patients were not relieved.

Eighteen of the fifty patients treated complained of side reactions, such as drowsiness, dizziness, weakness, dilated pupils, and dry mouth; in three, these reactions were severe enough to force discontinuance of therapy. Drowsiness, the most frequent ill effect, sometimes subsided when the dosage was reduced or after the drug had been taken for a few days.

Relief in general was apparent only while the drug was taken.

*The Symptomatic Treatment of Bronchial Asthma and Hay Fever with Benadryl* - When benadryl was used in the treatment of bronchial asthma by Koelsche *et al.*,<sup>4</sup> results were less encouraging than those obtained in patients with hay fever or hay fever associated with asthma. In the first

group, only four out of twelve patients experience relief, whereas thirty-nine out of fifty-two hay fever patients were benefited; in ten of these, relief was almost complete. In the group of nineteen patients with hay fever plus asthma, fourteen reported benefit and an additional five obtained relief of the hay fever symptoms but not of the asthma. Two of the five who failed to improve had to discontinue the drug before they had given it a fair trial because of side effects. Again, drowsiness was the predominating reaction, being reported by twenty-five patients. Several complained of nervousness; one patient experienced nausea and another facial edema.

***Use of Benadryl in the Syndrome of Physical Allergy of the Head—***

The comparative effects of benadryl and niacin on physical allergy of the head are discussed by Williams,<sup>5</sup> who considers the former superior in the treatment of perennial vasomotor rhinitis. Of twelve patients suffering from this condition, ten obtained striking relief when benadryl was given. The two who failed to benefit discontinued treatment after one dose because of extreme vertigo. Symptoms subsided markedly in four patients with hyperplastic ethmoiditis; they recurred, however, within twelve hours after the drug was withdrawn. While five myalgic patients experienced considerable benefit from the use of benadryl, they felt that the relief obtained from niacin was definitely greater. Two patients with Ménière's disease were observed. Both felt that their improvement on benadryl, while good, was less marked than on niacin and potassium nitrate.

In addition to drowsiness, side reactions reported were nervousness, vertigo, and inability to focus the eyes.

The author feels that benadryl is useful in physical allergy of the head, espe-

cially perennial vasomotor rhinitis, and that it should be tested further.

***The Use of Benadryl in Treating Some of the Allergic Diseases of Childhood—***Benadryl in capsules and elixir was used by Logan<sup>6</sup> in the treatment of allergic disease in eighteen children. Drowsiness and vomiting were the only untoward reactions encountered, and in the two cases in which vomiting occurred, there was a possibility that it may have been due to gastroenteral disease.

Twelve cases of seasonal hay fever, three of which had associated asthma, were treated. Relief of the hay fever symptoms was excellent or good in nine cases, fair in one, and questionable in another. The treatment failed in one case. Good results were obtained in one instance of associated asthma and fair results in another; in the third, relief was questionable. A child suffering from urticaria obtained prompt and marked benefit, but there was a recurrence of symptoms when the benadryl was discontinued. One case of vasomotor rhinitis was markedly improved; another obtained only slight relief but later reported improvement from an increase in dosage. Two cases of urticarial reaction, one to plasma and the other to tetanus gas gangrene antitoxin, were also benefited.

This author has found that, as a rule, an effective dose of the drug in children is 2 mg. per pound of body weight. He emphasizes the importance of adequate dosage.

***A Discussion of Benadryl as an Antihistamine Substance—***Code<sup>7</sup> reviews the literature on substances having antihistamine properties, and discusses the rôle of benadryl in the treatment of various allergic diseases, whose relationship is probably based on an abnormality of histamine metabolism. Its mode of

action in some of these disorders is not yet clear and should be studied further. While its action on the smooth muscle spasm and altered vascular reactions evoked by histamine have been reported, there is still a need to determine how much it interferes with other actions of histamine, as well as the exact site of its antihistamine effect. Benadryl's ability to relieve symptoms should not be regarded as proof that they are evoked by histamine. It is desirable that the blocking action of this substance to other biologically active compounds be investigated.

**Relief of Dermographism and Other Urticarias of Histamine Origin by a Synthetic Benzhydryl Alkamine Ether**—Because a new antihistamine substance, benzhydryl alkamine ether, had been efficacious in controlling cold urticaria, Feinberg and Friedlander<sup>8</sup> were prompted to prescribe it in three cases of urticaria factitia. The first dose caused a marked alleviation of symptoms, which recurred six to twenty-four hours after withdrawal of medication. The results led to an investigation of the effect of this drug on dermatographism, which had interfered with skin testing in thirty patients presenting clinical manifestations of allergy. When given prior to testing, positive reactions were elicited in eighteen of these patients. Failure to use it caused a return of the dermatographism. The only side effects noted were drowsiness and lassitude in some patients.

When administered to twelve cases of allergic rhinitis and seventeen cases of asthma, this benzhydryl alkamine was ineffectual. The striking results it brought about in cold urticaria failed to obtain in several cases of rhinitis and asthma precipitated or aggravated by cold. Two patients with chronic urticaria became almost asymptomatic when treated with

this substance, but two others failed to benefit. Relief was reported in several other cases of chronic urticaria, as well as in acute urticaria, serum sickness, chronic rhinitis, atopic and contact dermatitis, and pruritis.

**Histaminic Cephalalgia with Duodenal Ulcer**—A number of cases of histaminic cephalalgia with concomitant peptic ulcer have been reported, and Alford and Whitehouse<sup>9</sup> suggest that the latter syndrome may be induced by increased gastric acidity during the cephalalgic attacks. To support this contention, they present a case in which the histaminic cephalalgia had its onset fifteen years previously, with symptoms of peptic ulcer developing three years later. The gastric flare-ups occurred coincidentally with the headaches.

Studies revealed evidence of an ulcer in the first part of the duodenum, with crater formation. It is interesting to note that contrary to most cases of active peptic ulcer, gastric acidity was very low following a test meal of broth. Administration of 0.5 mg. of histamine phosphate caused a sharp rise in total and free hydrochloric acid values without evoking a headache. The acid curves during spontaneous attacks of histaminic cephalalgia seemed to parallel the onset, severity, and termination of the headache. There was no significant difference between total and free acid values, as noted after treatment with histamine or following an attack of histaminic cephalalgia.

Treatment with histamine, combined with ulcer therapy, resulted in a complete disappearance of symptoms. Essential gastric secretory function seemed unaffected.

### Diagnostic Tests

**Skin Sensitivity in the Aged Fatality Following Intradermal Tests**—

The skin in older persons, or in those with allergic disease of long duration, is generally thought to be nonreactive. However, Wiseman and McCarthy-Brough<sup>10</sup> report the case of a seventy-eight-year-old woman in whom intradermal tests, which had elicited many marked skin reactions, were followed by death.

The patient gave a history of asthma since the age of four. She was worse during the fall and winter. The attacks were precipitated by milk, pork, cabbage, and exposure to a cat. They were aggravated by upper respiratory infections. Avoidance of offending proteins and a course of *dust* and *vaccine injections* resulted in such marked improvement that she discontinued treatment (after attaining a dosage of 1 cc. of each) for about three years. Weakness, loss of weight, and an exacerbation of asthmatic symptoms then prompted resumption of the dust and vaccine injections and, three weeks later, repetitions of intradermal tests made six years earlier. Extracts of coffee and various inhalants, in amounts of 0.01 to 0.02 cc., were used. The patient also received injections of 0.35 cc. of house dust and 0.3 cc. of stock vaccine at this time. Cough and moderately severe dyspnea began about five minutes later. Despite the subcutaneous injection of epinephrine, the patient became cyanotic and lost consciousness. Intravenous epinephrine, oxygen, artificial respiration and, finally, epinephrine injected into the heart, were without avail. Death occurred about fifteen minutes after the tests were made.

**The Diagnostic Value of the Eosinophile in Allergic States**—In studies of sixty nasal smears and thirty-nine blood smears from allergic individuals, Mansmann<sup>11</sup> noted an eosinophilia ranging from 5 to 20 per cent, and reaching, at times, 35 per cent. In only three or four instances was this phenomenon ob-

served without a demonstrable allergic basis. However, since it is sometimes seen in other disorders, such as parasitic infestations or various tropical diseases, the presence of such disease necessitates caution in interpreting the eosinophilia as being due to allergy.

The author points out that allergic symptoms may simulate acute or chronic infection, and emphasizes the importance of nasal smears as a diagnostic medium. Attention is called to the fact that the nature and location of the allergy sometimes determine the tissues or secretions on which eosinophile counts should be made (*e. g.*, the stools, in gastrointestinal allergy; the urine, in urinary system allergy; sections of nasal polyps; antral washings, etc.).

The characteristics of the eosinophile are outlined and methods are presented for taking, preparing, and interpreting nasal smears.

#### **The Conjunctival Test as a Guide to Clinical Immunity in Hay Fever—**

The conjunctival threshold of reaction to pollen extract was tested by Lovelless<sup>12</sup> in ninety-five patients. Prior to a course of ragweed extract injections, a preliminary test was made on one eye, beginning with a pollen extract containing 1 P.N. unit per cc. and continuing with extracts of gradually increasing strength, until the first reaction point was passed. After the course of treatment, the other eye, which had previously served as control, was tested, beginning with the strength just below the one previously eliciting the reaction. Reactions occurred to solutions containing from 15 to 4000 units; in the majority of cases, irritation became apparent with the use of extracts of 50 to 400 units. When clinical results were compared with threshold responses, it was found that 95 per cent of the patients with thresholds of 350 to 500

were markedly benefited, and symptoms were satisfactorily relieved in only 49 per cent of those with thresholds of 35 or less. Since better clinical results seem to be attained with higher conjunctival thresholds, it is suggested that until a new patient's own "protective" threshold is established, it may be well to give booster courses adequate to raise the threshold to at least 300, if possible. The test should be valuable as an index of the amount of treatment required.

### Hay Fever

**Treatment of Ragweed Pollinosis with Antigen-Antibody Mixtures—**Very satisfactory clinical results were achieved by Cohen and Friedman<sup>13</sup> in three cases of asthma with exacerbations during the ragweed season, by three to four injections of an approximately neutral mixture of thermostabile antibody and pollen extract. The material was prepared by injecting normal individuals, at weekly intervals for four weeks, with gradually increased doses of a 10 per cent ragweed extract. The subject was bled if the titer was considered high enough by determination of serum obtained seven days after the last injection; if not, another injection of ragweed was given three weeks later, and the bleeding was then done. When the globulin had been titrated for its thermostabile antibody content, ragweed extract was added in an amount considered sufficient to be neutralized by this antibody. The mixtures were tested for the presence of free antigen. Those containing between 10 and 100 P.T.A. units per ml., as determined by titrating the skin of ragweed-sensitive patients, were regarded as neutral or practically neutral. They failed to evoke systemic reactions caused by too rapid dissociation of the antigen and antibody, when injected into individuals sensitive to ragweed, even in

doses containing as high as 6000 units of neutralized antigen.

To test the capacity to produce a high thermostabile antibody titer, a nonragweed sensitive subject was given three injections of such a mixture, at four-day intervals (20,000 P.T.A. units of "neutralized" extract, or the estimated equivalent of 600 to 700 P.T.A. units of unneutralized extract). He showed a thermostabile antibody titer three weeks later of 750 units.

This material, when administered to the three ragweed-sensitive patients, resulted in almost complete absence of the seasonal exacerbations previously experienced.

**Vitamin C in Hay Fever: Therapy and Blood Levels—**Ascorbic acid in a daily dosage of 500 mg. was given by Friedlander and Feinberg<sup>14</sup> to forty-three hay fever sufferers, nine of whom had concomitant seasonal asthma. The treatment was carried out during the hay fever season and varied in duration; in most cases, it was begun by August 15th and continued for two to six weeks.

Pollen hyposensitization had been unsuccessful in twelve of the cases, and the others had received very little or no previous treatment.

There was no alleviation of asthma as a result of the vitamin C therapy. Only three patients reported relief of hay fever symptoms, and in at least one of these the rôle of the treatment is questionable, since the patient suffered a recurrence of symptoms when the vitamin was omitted, but again improved on taking placebo tablets of the same size and shape.

The vitamin C blood levels of hay fever and normal subjects were similar. A normal saturation point was attained in the blood levels of treated hay fever patients, despite their failure to derive clinical benefit.

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tervals resulted in the appearance of urticaria twenty-four days after treatment began. It involved the face and neck first, and then became generalized. Each succeeding injection intensified the condition, and the drug was discontinued the following day. The urticaria continued unabated for three days longer, but by five days after cessation of therapy it had disappeared.

Attempts to determine the least amount of penicillin that would produce the urticaria showed that during the eleven-day reactive phase, as little as 50 units of commercial penicillin sodium provoked a response; afterward, injections increasing to 20,000 units could be tolerated. Skin and passive transfer tests were positive during the reactive phase, but negative after it. There were no reactions to penicillium extract at any time.

This case suggests that the reactive effect of penicillin may be transitory. While it is not clear whether the subsequent negative response was spontaneous or due to gradually decreasing the dosage, it may be that in cases of severe penicillin urticaria, desensitization can be attained by graduated doses of the drug.

**Urticaria Following the Use of Protamine Zinc Insulin**—Protamine zinc insulin was responsible for the development of urticaria in a case observed by Hughes and McAlister.<sup>19</sup> The patient had previously taken regular insulin without difficulty. Both direct and passive transfer tests failed to show sensitivity to this type of insulin, but definite reactions were elicited with protamine zinc insulin made from beef and pork pancreas, as well as with a preparation containing insulin from pork pancreas only. The conclusion that protamine (salmine) was responsible for the urticaria could not be substantiated by skin

tests because a sterile sample was unavailable.

Skeptophylactic deallergization was attempted by two methods: (1) Administration of  $\frac{1}{2}$  unit of each regular and protamine zinc insulin, forty five minutes before the regular doses, for three days, and (2) giving one unit of protamine zinc insulin and increasing the dosage by one unit every fifteen minutes until a dosage of eight units was reached (thirty-six units in all); then fifteen units of regular insulin, followed by breakfast this was carried out for four days. When these attempts failed, injections of histamine azoprotein were given at three day intervals, in gradually ascending doses beginning with 0.1. Results were highly satisfactory.

### Bronchial Asthma

**Carcinoma of the Lung with Asthmatic Symptoms** To support the fact that "all that wheezes is not asthma," Moore<sup>20</sup> describes four cases of bronchogenic carcinoma which closely simulated bronchial asthma. The patients had been diagnosed and treated as asthmatics, and there had been some response to epinephrine, etc. In three cases, the lung carcinoma was revealed after death; in the fourth, it was demonstrated by biopsy of a growth observed on bronchoscopic examination.

The author points out that in diagnosing cases of this type, one is most prone to err during the period of partial obstruction with segmental emphysema. During the last stage of atelectasis, the asthmatic symptoms disappear, but by then it is too late for lobectomy. Unfortunately, x ray findings are frequently misleading; the history, clinical signs, and, if carcinoma is suspected, bronchoscopy, are far more important diagnostic measures.



As an aid to differential diagnosis, the distinctions between allergic bronchial asthma and bronchogenic carcinoma are outlined.

**Spontaneous Mediastinal and Subcutaneous Emphysema Complicating Bronchial Asthma**—According to Schwartz,<sup>21</sup> the incidence of spontaneous mediastinal and subcutaneous emphysema is much greater than is commonly believed. It has occurred in influenza and other respiratory diseases, as well as during or following conditions which involved various types of physical strain.

This investigator describes one case which he observed and discusses twenty-five previously reported cases, in which it was a complication of bronchial asthma. As a rule, the emphysema appeared first in the neck and then in the face and chest, and, in a few cases, the arms. The abdomen and thighs were seldom involved. Duration averaged nine days, with a range of two days to three weeks. There was only one report of a recurrence; this occurred a year later. One worker effected release of air by the insertion of a needle, but all other cases responded to conservative treatment.

In Schwartz's patient, the extreme dyspnea and wheezing which had previously failed to respond to ephedrine, adrenalin, intravenous aminophyllin, and oxygen, were alleviated with the appearance of the subcutaneous emphysema in the neck. This sudden improvement has been noted by other workers, and is thought by Macklin and Macklin (1943) to be caused by relief of mediastinal circulatory distress.

The author points out that spontaneous pneumothorax, while a rarer complication of bronchial asthma than subcutaneous emphysema, is a much more serious one, and, according to reports, has a mortality of about 25 per cent.

**Inhalation of Penicillin Aerosol in Patients with Bronchial Asthma, Chronic Bronchitis, Bronchiectasis, and Lung Abscess**—Twenty patients with bronchopulmonary infections were treated by Barach *et al.*<sup>22</sup> with penicillin aerosol, produced by passing from 20,000 to 100,000 units of penicillin in 1 cc. of physiological saline through five to eight physiological saline through 5 to 8 liters of oxygen. Treatment was administered four to five times a day, for an average of sixteen days, by means of a nebulizing apparatus permitting the reinhalation of some of the expired aerosol along with that nebulized during inspiration. However, it is stated that any small nebulizer producing particles less than 1 micron in diameter may be used.

Four patients complained of slight and transitory substernal soreness, but x-rays made routinely before and after treatment failed to reveal signs of irritation. Ten normal and miscellaneous controls exposed to inhalations of the aerosol experienced no distress. No definite irritation was evidenced by comparing histopathological sections of lung tissue from normal and repeatedly-treated rats.

Blood levels within fifteen minutes to one hour after treatment averaged 0.01 to 0.04. A higher blood level is attained when a deep breath is taken at inspiration and held for several seconds; however, the aim in the treatment of bronchial infection seems to be local application of the drug rather than high blood levels. Sputum cultures twenty-four hours after termination of treatment were negative for the predominating organisms found in specimens taken before treatment. Ten to 20 per cent of the aerosol inhaled was excreted in the urine in twenty-four hours.

As a result of the inhalations, four patients with bronchial asthma were asymptomatic for one to two months. A

second course of treatment when symptoms recurred aborted them again in two of these patients, but was without benefit in the other two. One patient with bronchiectasis and one with undiagnosed pneumonitis were also markedly relieved. There was moderate improvement in eight cases of bronchial asthma with bronchial infection and either pulmonary emphysema or bronchiectasis, although symptoms recurred approximately one month after treatment stopped. One case of lung abscess and one of advanced bilateral bronchiectasis were thought to have derived some benefit.

The inhalations failed to improve a lung abscess with closed cavity, two cases of bronchiectasis with chronic lung abscess, and two of advanced pulmonary fibrosis.

**Combined Helium and Epinephrine Therapy**—Wickner<sup>23</sup> describes a simply operated and, if desired, portable apparatus for combined epinephrine and oxygen-helium therapy. Conversion from epinephrine administration to the oxygen-helium mixture is easily accomplished by means of a slide diaphragm, though it is hoped that some device can be developed to permit simultaneous use of the vapor and gases. A rebreathing unit with a circle filter prevents wasting expensive gases, with a consequent saving in the cost of operation. An added advantage is the fact that other vaporizable material can be used, thus permitting administration of combined inhalation therapy in various combinations of gases and vapors.

The apparatus has been found valuable in office treatment of acute asthmatic seizures, and such treatment causes no interference or blocking effect in skin tests.

**Asthma and Bronchial Infection Treated with Penicillin**—Two pa-

tients exhibiting asthma with bronchial infection were treated with penicillin by Derbes and Wilson.<sup>24</sup> Injections were given intramuscularly at four hour intervals, in a total of 500,000 units.

The first case, of nineteen years' duration, experienced considerable relief of clinical symptoms, but x ray findings before and after treatment were similar. In the second patient, the disease had been present for two years. Here, marked clinical improvement was accompanied by considerable clearing of the pneumonitis which had been present.

It is concluded that penicillin is valuable in the treatment of this type of asthma, but, like other therapy, it should be given early for maximum benefit.

**Sputum Cholesterol in Bronchial Asthma**—Sputum cholesterol determinations in fifty-one patients with bronchial asthma were found by Fuchs *et al.*<sup>25</sup> to range from 7 to 55 mg. per cent (1 to 10 mg. of cholesterol). No correlation was apparent between cholesterol value and age, duration of symptoms, or volume of a twenty-four-hour specimen of sputum. Severity of clinical symptoms, however, definitely influenced the cholesterol content of the sputum. The majority of cases ranged from about 25 to 55 mg. per cent in the skin-negative, infective group; 7 to 25 mg. per cent in the skin-sensitive group, and 20 to 30 mg. per cent in the group showing skin sensitivity and chronic respiratory infection. The cholesterol elevation noted in the sputa of patients with chronic, persistent asthma is believed due to the large amounts of ephedrine and epinephrine taken for relief.

### Unusual Sensitizations

**Endocrine Allergy—I. Allergic Sensitivity to Endogenous Hormones**—Zondek and Bromberg<sup>26</sup> have demonstrated that in certain gynecologic

disorders or premenstrual flareups of allergic diseases, there is a sensitivity to endogenous hormones or their metabolites. They term this "endocrine allergy."

Tests were made with seven steroid hormones (estrone, estradiol, progesterone, pregnandiol, testosterone, androsterone, and desoxycorticosterone acetate). Individuals with negative skin reactions were further tested with insulin and prolan. The 165 subjects were subdivided as follows: (a) Normal controls; (b) allergic diseases related to menstruation; (c) pruritis vulvae and acne related to or aggravated by menstruation; (d) premenstrual tension; (e) dysmenorrhea during menstruation; (f) allergic disease related to menopause; (g) pruritis vulvae related to menopause; (h) allergic diseases, pruritis vulvae and acne not related to menstruation or menopause. Skin reactions were negative in group *a* (32 women) and in group *e* (11 women). In group *h*, positive skin reactions were observed in only 2 of the 26 women tested. Of the 96 remaining cases, 66 showed positive skin reactions, and 4 developed general reactions as well, such as vomiting, urticaria, vertigo, fever, metrorrhagia, etc. All 4 were subsequently desensitized. Many of those reacting gave personal and hereditary histories of allergy, and there was a high incidence of eosinophilia in this group.

In several cases, positive skin reactions were delayed until the premenstrual period. Two patients experienced recurrences of reactions at the test site during the premenstrual phase of six successive periods. A subcutaneous injection of the allergenic hormone, given twenty-four hours after the test, elicited a local reaction at the test site. Normal subjects injected intracutaneously with serum of estrone-sensitive patients showed positive skin reactions following subsequent in-

jections of estrone given at the same site. Also, positive skin reactions occurred in normal subjects who had received injections of serum from estrone-sensitive patients, when the allergenic hormone in their bodies reached a peak, either during the premenstrual phase or as a result of a subsequent injection.

Desensitization by the administration of gradually ascending doses of the reacting hormone was attempted in forty-four cases. There was a complete disappearance of symptoms in twenty-two, and definite improvement in thirteen others. Nine patients were not benefited.

**An Unusual Effect of Aminophyllin on the Intestinal Tract**—The antispasmodic effect of aminophyllin on an allergic bowel was noted by Zeller<sup>27</sup> in a woman with a history of bronchial asthma, hay fever, gastrointestinal symptoms, and frequent headaches. An appendectomy and a cholecystectomy had failed to alleviate the abdominal distress, and two additional laparotomies relieved the acute attacks only. Aminophyllin, administered intravenously during an asthmatic seizure, not only relieved the respiratory distress but caused a disappearance of marked abdominal distention. It was given subsequently for the relief of abdominal distention, pain, and pressure. Particularly striking was the benefit obtained from symptoms of acute intestinal obstruction, which had been unrelieved by intubation, enemas, and other palliative measures. The abdominal symptoms failed to respond to injections of epinephrine or to oral aminophyllin in a dosage reaching 1.7 gm. (25 grains) a day. On the contrary, more than 0.5 gm. (8 grains) of aminophyllin daily, when given orally, intensified the distress.

There was no passage of flatus following an injection of the drug, and it is suggested that the abdominal collapse

may be due to a redistribution of gas in the bowel.

The clinical response noted was borne out by x-rays made before and after the injection of aminophyllin. There appeared to be no effect on the gallbladder.

**Allergy to Tobacco Smoke**—When the records of 370 allergic individuals were examined, Pipes<sup>28</sup> found that in 35 the symptoms were precipitated or aggravated by tobacco smoke. In 47 patients, there were positive reactions to skin tests with tobacco smoke extract, and in 19 it was possible to correlate the positive skin reactions with the clinical history. Control tests with tobacco smoke extract on 10 normal individuals were negative. Passive transfer sites of tobacco-sensitized serum, while completely exhausted with tobacco extract, were reduced only 30 to 40 per cent with tobacco smoke extract. Likewise, although passive transfer sites of tobacco smoke-sensitized serum were exhausted by tobacco smoke extract, a reduction of only 40 to 50 per cent was attained with tobacco extract.

It was concluded that allergy to tobacco smoke may be a distinct entity, exclusive of allergy to tobacco. The use of extracts of both in routine skin testing is recommended.

**Sensitivity to the Oral Administration of Castor Oil**—The literature contains many reports of contact sensitivity to castor oil and inhalant sensitivity to castor bean dust. However, a case observed by Blank<sup>29</sup> probably represents the first report of sensitivity to oral administration of castor oil.

The patient, age twenty-three, could remember no reaction to castor oil taken in childhood, and presented no history of allergy, except that a maternal uncle had fall hay fever. Marked generalized abdominal cramps and diarrhea developed within twenty minutes after

ingestion of 1 ounce of castor oil. Within two hours, the tongue and fauces became red and edematous and there was marked facial flushing, followed by a scarlatinous rash extending down over the shoulders, as well as edema of the eyelids, lips, and ears, stomatitis, and abdominal tenderness. Temperature and pulse rate were somewhat elevated. A little later conjunctivitis and rhinorrhea developed, a punctate vesicular papular rash appeared on the neck and shoulders, and the erythema became generalized.

By the following day there was a marked alleviation of symptoms. Desquamation began in forty eight hours, and complete recovery was attained in four days.

Three days later the patient received 4 cc. of castor oil orally. All symptoms recurred, in a slightly milder form. After three weeks, the clinical test was repeated, using only 1 cc. of oil. This time the exacerbation which followed was definitely less severe.

A leukocyte count showed 5800 cells and there was an eosinophilia of 6 per cent. Reaction to a scratch patch test with castor oil was slight. There was no reaction to a patch test.

**Allergy to Chemicals in Flour. A Case of Dermatitis Due to Benzoic Acid**—Severe dermatitis and periodic asthma in a baker observed by Baird,<sup>30</sup> at first attributed to wheat, were later found due to residual traces of benzoic acid from benzoyl peroxide used as a flour "improver" or bleach. The patient had shown positive skin test reactions to wheat protein. Attempts at hypo-sensitization failed, as did injections of a mixed, sensitized vaccine. Freedom from contact with flour during a two-week period of hospitalization (preceding which he had been asthma-free for several weeks), and elimination of wheat

from the diet, resulted in complete clearing of the skin. The dermatitis recurred on subsequent exposure.

Patch tests with the three types of "improved" flours used by the patient evoked a typical rash, but reaction to the one nonimproved type was negative. There were no reactions to patch tests with aqueous solutions of benzoic acid and potassium bromate (traces of the latter are frequently added when flour is bleached). A definite papular rash resulted from patch testing with 6 per cent benzoic acid in liquid petrolatum; no response was elicited in a control test with petrolatum alone.

Despite inclusion of wheat bread in his diet, the patient had experienced no difficulty since changing to nonimproved flours, except for an occasional slight papular rash. In this connection, it is interesting to note his feeling that some skin reaction follows handling or eating commercial jams and pickles, in which sodium benzoate is frequently used as a preservative.

### Fungi as Allergens

**Air-borne Fungi in Allergic Disease. I. A New Method of Preparation of Mold Extracts; Incidence of Skin Reactions with Mold Extracts**—A new method of preparing mold extracts by the process of spore germination, where a ball mill is not available, is described by Hampton and Lowe.<sup>31</sup> This method was used in the preparation of four mold extracts from spores collected by these workers during a three-month survey of the mold content of the air in the vicinity of San Antonio, by the plate method. The extracts individually, as well as a pooled extract of the 4, were tested on 358 allergic patients and 92 normal controls. Incidence of positive skin reactions was as follows: Pooled extract, reactions obtained in 57 of 358

patients tested; *Alternaria*, in 55 of 358; *Hormodendrum*, in 21 of 301; *Spondylocladium*, in 33 of 259; *Helminthosporium*, in 14 of 101. All the controls were negative.

Of the 57 reacting patients, 16 gave positive reactions also to pollen extracts, 21 to inhalants, and 4 to foods. Fifty-four had clinical symptoms of hay fever, vasomotor rhinitis, and bronchial asthma, and in 47 of these, eosinophilia was demonstrated in nasal smears.

In appraising the relationship between the positive skin reactions and spore counts, it is a point of interest that although *Hormodendrum* predominated in the counts, it caused the smallest percentage of reactions, whereas *Alternaria*, while present in lesser numbers, provoked the greatest. Cultures of *Spondylocladium* and *Helminthosporium* were rare, yet each was responsible for almost double the reactions (by per cent) as those caused by *Hormodendrum*.

**A Study of the Fungus Contaminants of the Air of San Diego and Vicinity**—The fungus content of the air in and around San Diego was studied by Harsh and Allen<sup>32</sup> over a period of three years, by the gravity slide and culture plate methods. During the first and third years, counts were made from slides and plates exposed on top of a two-story building in central San Diego. In the intervening year, three additional collection points were established: At the beach, at the eastern city limits, and at Alpine, California (thirty-two miles inland at an elevation of 2300 feet).

A total of 131 species, of 27 genera, was isolated. Those most prevalent were *Hormodendrum*, *Alternaria*, yeasts, *Macrosporium*, *Sporotrichum*, and *Helminthosporium*. Some genera seemed to occur sporadically throughout the entire area; in some, the incidence increased from the coast inland, while in others it

decreased. Also, there were some in which the counts rose or fell as one proceeded inland, except in the mountains, where the reverse was true. It was noted that molds requiring a damp cool climate for best growth, such as *Penicillium*, diminished in number from the coast inland.

Extracts of the molds obtained were prepared and used in skin testing 153 allergic individuals. Positive skin reactions were noted in 61 per cent of 36 children tested, and in only 25.6 per cent of 117 adults. Such differences have been reported also by other workers, and are contrary to results obtained in tests with pollen extracts, where age does not appear to be a factor. No definite explanation is offered, but attention is called to the fact that mold sensitivity in a child is frequently outgrown.

It seemed desirable to have some index of the amount of allergen available for absorption by patients. Therefore, determinations were done of the total nitrogen and protein nitrogen of the predominating molds, as well as estimations of their comparative rate of solution. In addition, the approximate size and shape of the mold spores was determined, and these data were used, with corrections for other physical characteristics of the spores and for atmospheric conditions, to calculate the mass of allergen in a unit volume of air.

**Mold Allergy—I. Field Survey of Philadelphia Area.**—Results of a survey by Blumstein and McReynolds<sup>33</sup> indicated that the major mold season in the Philadelphia area lasts from mid-May to mid-October. Spore counts were obtained in the center of the city by the gravity slide and culture plate methods. Correlation was not attempted, but it was felt that more information would be derived by using both methods than either one alone. Direction and velocity of the wind

seemed to have no influence on the number of spores obtained. A possible explanation is the apparent absence of primary mold-producing sites in this vicinity. Rainfall seemed to result in a decrease. There was a time variation, the highest number being found on plates exposed in the early afternoon. The warmth and moisture of spring and summer seemed conducive to rapid growth, with a resultant increase in count, and frequent spore showers were noted, especially during the fall. The most striking seasonal variation was in the molds with large and distinctive spores (*Alternaria*, *Hormodendrum*, smuts, rusts, *Helminthosporium*, and *Fusarium*). Counts on these were radically elevated during the period which was established as the major mold season.

**II. Clinical Analysis** It has long been recognized that molds play an important part in provoking allergic symptoms, but the incidence of mold allergy is still controversial. In tests with 13 mold extracts, Blumstein<sup>34</sup> observed that 169 out of 406 patients showed positive skin reactions to 1 or more of them. Checks *via* the nasal route, using a mold powder corresponding to the extract evoking the positive skin reaction, caused symptoms of hay fever in 12 patients. In the order of their importance, the molds most generally producing reactions were *Alternaria*, *Hormodendrum*, *Monilia*, *Helminthosporium*, *Cephalosporium*, and *Mucor*. It is suggested that extracts of these be used for tests where mold sensitivity is suspected.

All 12 of the patients reacting to the nasal test were seasonal cases. Ten were asthmatics and the chief complaint in the other 2 was seasonal rhinitis. Satisfactory relief was achieved by treatment mild mold extracts. In 8 of these cases, pollen sensitivity was an additive factor. As a point of differen-

tiation, it was noted that whereas irritation of the eyes is usually constant and annoying in pollen sensitivity, this symptom constitutes a minor complaint in mold allergy. Moreover, the symptoms in mold allergy are manifested throughout the major mold season, lasting from May to October, whereas there is a period of remission between the grass and weed seasons in pollinosis.

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## ANESTHESIA

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## Operative Risk

It is well recognized that the severely burned patient does not present an uncomplicated picture, including when he is a candidate for administration of anesthesia. Papper<sup>1</sup> has made some interesting observations on the effects of various anesthetic agents by studying a series of burned patients during the postoperative period. On a comparative basis, one of his first observations made was that the viability of the graft apparently was unaffected by the type of anesthesia administered. Also, while the blood pic-

ture showed no gross change following either spinal or regional anesthesia, it showed a moderate decrease in both the erythrocyte and hemoglobin estimations in those individuals to whom pentothal sodium had been administered. On the average, 500 cc. of whole blood was required for a patient in the immediate postoperative period in these instances. Following the administration of ethyl ether, a more profound anemia occurred, which required an average of three blood transfusions of 500 cc. for each patient in a similar period of time. On the basis of the amount of whole blood required

to restore a minimum of 3,500,000 red blood cells per cm. with a corresponding normal concentration of hemoglobin for this level of red cell count, he drew the conclusion that where general anesthesia was required for skin grafting in the treatment of burns, intravenous pentothal sodium exerted a less harmful effect upon the patient than did ethyl ether.

Observations made on the effect of drugs of the sulfonamide group given both preoperatively and postoperatively, before a period of pentothal sodium anesthesia, showed no ill effects nor any synergism between the two. In addition, he believes that it is safe to administer sulfonamide drugs prior to operation in the treatment of burned patients regardless of the anesthesia to be administered subsequently.

Papper claims that the use of morphine for the relief of pain in severely burned patients constitutes the safest and most advantageous treatment. In exceptional cases, he admits, small doses of pentothal are acceptable, but warns against the use of spinal anesthesia if the burned areas involved are above the tenth thoracic segment, because of the danger of the attendant circulatory depression produced by this type of anesthesia in a patient whose blood circulation may already have been impaired by his condition.

### Preanesthetic Sedation

Following an experimental investigation on dogs, Robbins<sup>2</sup> writes that there is a definite advantage in the use of demerol over morphine as a premedicating agent for cyclopropane. While he found some reduction usually in heart rate and a temporary fall in blood pressure after the injection of demerol, the cardiac irregularities which can and do develop with this agent after morphine premedication were not observed; at the

same time, he believed that demerol makes necessary a smaller amount of cyclopropane in order to institute lighter planes of anesthesia.

Beecher<sup>3</sup> points out the dangers of excessive doses of morphine in individuals of small stature or in those weakened by wounds contributing to an interference of the mechanism for intake and distribution of oxygen. It is his impression that the drug should be considered indicative for the relief of severe pain only, and it should not be used in restlessness associated with anoxia due to hemorrhage or hysterical states. The drug is not particularly indicated in shock, except where the pain is severe.

A note of caution toward the use of the barbiturates is explained by Alvarez.<sup>4</sup> He believes that these drugs are contraindicated in patients exhibiting a neurotic or psychoneurotic behavior, for in this class of patients they may produce excitement or mental discomfort.

For obstetrics, Irving<sup>5</sup> praises the combination of demerol and scopolamine. In calling attention to the disadvantage in the possibility of pulmonary complications when using barbiturates with scopolamine, he showed that nembutal produced respiratory complications in 35 of 10,007 patients, while the same complication occurred in only 9 of 4579 patients after seconal and amytal sodium. For patients who become overexcited from the effects of scopolamine, he recommends the administration of 100 mg demerol intramuscularly, or the use of a retention enema containing 2 drams of paraldehyde, 2 ounces of ether, and 2 ounces of oil. He concludes that by substituting demerol and scopolamine for a barbiturate prior to the use of general anesthesia, a 20 per cent increase in the number of babies who breathed spontaneously and immediately resulted.



A more or less isolated report of four instances of massive edema of the uvula and glottis was reported by Steinberg.<sup>6</sup> Because one of these occurred in a patient after the use of seconal-scopolamine combination and three as a result of demerol-scopolamine obstetrical analgesia, the author suggests that scopolamine may have been the etiological agent. However, rather large doses of all were used.

### Inhalation Anesthetics

**Nitrous Oxide**—The dangers of oxygen want during nitrous oxide anesthesia should continuously be emphasized.<sup>7</sup> Andrews, in 1868, first recommended that oxygen mixtures should always be employed with nitrous oxide. His long since forgotten advice in this respect was founded on experiments with rats. Before his time, it was believed that the body, in some way, could split oxygen from the nitrous oxide molecule and utilize it. Since his time, many advances have been consummated. Procedures for the convenient administration of nitrous oxide that have been developed progressively from the time of its first use consist of the preparation of the gas compressed in metal cylinders, the development of apparatus for its administration, and the use of rebreathing and the carbon dioxide absorption technic, together with many safety accessory appliances.

As far back as the year 1886, Hewitt found that anesthesia could be maintained with nitrous oxide when given with a concentration of oxygen approximating that in the surrounding atmosphere. Although this contributor recommended a 7 per cent oxygen mixture with nitrous oxide that produced a rapid induction and a state of anesthesia of 50 seconds' duration, it is not considered likely that this suggestion was

made with the idea that it would be adopted later for operations lasting more than an hour.

Impetus to nitrous oxide oxygen anesthesia here in the United States was accelerated by the work of Teter, who developed a popular gas oxygen apparatus which was supplied with instructions to use 5 to 10 per cent concentrations of oxygen with nitrous oxide, to disregard cyanosis, and advocating the state of anoxemia as being essential to gas anesthesia. A little later McKesson recommended both the induction of anesthesia with 100 per cent nitrous oxide and, his primary and secondary saturation technic, employing definite and pronounced oxygen lack, although temporary in nature.

In spite of the refinements of administration and of equipment for modern technics, morbidity and mortality associated with the use of nitrous oxide has increased to the point where some believe that although this gas was regarded as the safest of all anesthetic agents around the turn of the century, it has now become one of the most, if not the most, dangerous at the present time. While it cannot be ignored that the agent itself has not been found to produce any significant or demonstrable degree of toxicity in any tissue in the human body, it appears to be just as factual that many of the fatalities following anesthesia with its use are due either to technical errors during its administration or an improper use of the agent.

The greatest detriment to the use of nitrous oxide is its usual accompanying lack of potency. Only a small percentage of individuals, when given nitrous oxide with a concentration of oxygen comparable to that present in atmospheric air, will show a condition identified at the present time as surgical anesthesia, because of the usual absence of muscu-

lar relaxation. Best anesthesiological practices demand today that a combination of pain relief and muscular relaxation should be instituted where indicated without oxygen deprivation. Many findings substantiate the fact that oxygen want does develop during nitrous oxide oxygen anesthesia usually, and especially where muscular relaxation is necessary. Kemp, Leake and Hertzman, Green *et al.*, as well as Brown, Lucas, and Henderson, state that patients anesthetized by nitrous oxide will always suffer from a severe degree of anoxemia. McQuiston, Cullen, and Cook believe, with many others, that any appreciable reduction in oxygen below 20 per cent may become extremely dangerous to the patient. If patients can be satisfactorily anesthetized only *after adequate sedation* by the use of not more than 80 per cent nitrous oxide, the procedure may be considered safe, for as Raginsky and Bourne found, the blood oxygen content was within safe limits when these concentrations were used in man. That it can be done has been shown by Cullen and his associates, who do not use any mixture containing less than 20 per cent oxygen. This type of application, however, demands adequate sedation and a hospitalized patient, which is not usually possible in the private office of a physician or a dentist, or in a hospital outpatient clinic.

According to the exhaustive works of Courville, which might aptly be reviewed here, fatalities from nitrous oxide anesthesia may be divided into several groups. The first of these includes patients who die during anesthesia; here death may be attributed to a preexisting lethal lesion, to a secondary lesion independent of the surgical one, to a combination of disease and asphyxia, and, finally, due to the direct anoxic effect of the anesthetic agent itself, in which

last group no characteristic pathologic condition can be found at autopsy. In the latter group, the cause of death has many times been ascribed to status thymico-lymphaticus, idiosyncrasy, or anoxemic depression of the respiratory center. In the second group, there is initiated under anesthesia by anoxemia a process that progresses until a situation is reached that is incompatible with life, which situation may occur hours or months after administration of anesthesia. The third group are those that recover but retain mental symptoms which are indicative of cortical nervous system damage. The final group includes individuals who exhibit transitory mental and emotional disturbances, such as visual and auditory manifestations, aphasia, convulsive states and delirium, but which ultimately recover.

It has been established that the brain is the portion of the body that is the least resistant to anoxia. It is agreed that the lesions most likely to occur include (a) sclerosis of scattered pyramidal nerve cells, (b) patchy necrosis, (c) degeneration of various cortical layers, (d) subtotal destruction of limited portions of the cortex, and (e) similar lesions in the lenticular nucleus.

Second to the brain, the heart is the organ most sensitive to anoxia. When a patient is under anesthesia who has had coronary sclerosis or unrecognized myocardial disease, an acute coronary insufficiency due to anoxia may develop during nitrous oxide anesthesia without the usual warning signal of pain.

In conclusion, when anoxia has developed with nitrous oxide oxygen anesthesia, there have been produced (1) death from asphyxia, (2) psychoses from permanent brain damage, (3) personality defects, and (4) impairment in circulatory and respiratory function. Therefore, it would appear that nitrous oxide

should never be administered with oxygen in concentrations below 20 per cent.

**Cyclopropane**—The use of this agent apparently is not suffering from a decrease in popularity. It permits a more rapid control of the level of anesthesia than that provided by any of the commonly used inhalation agents.<sup>8</sup> Deeper levels of anesthesia can be more safely instituted possibly by supplementary measures, such as curare or intercostal block anesthesia. The pulse rate under deep cyclopropane anesthesia, when administered by skilled individuals, is usually reduced to between sixty to seventy beats per minute. A rapid induction with nitrous oxide and cyclopropane combined, turning to unsupplemented nitrous oxide anesthesia or premedication with scopolamine or atropine, apparently prevents or minimizes hyperactivity of the autonomic reflexes during its use. An example of its comparative value can be provided by citing its use for eleven consecutive hours in a sixty-year-old patient undergoing extensive abdominal surgery.<sup>9</sup> Within one hour after cessation of anesthesia, the patient was awake and rational, although death occurred on the fourth postoperative day due to a combination of the patient's disease, a left pneumothorax, emphysema of the left chest wall, and an early pneumonic infection in the left lung.

### Inhalation Technic

In an effort to render more safe the use of ether where surgery demands the use of high frequency current for electric coagulation, especially during long operations on the spinal column when the patient is in the prone position, or in operations about the head and neck, Saklad<sup>10</sup> has described a new technic. Induction is carried out in the usual manner with a closed circle type of apparatus after which intubation is insti-

tuted. The flow of ether is then increased, the expiratory tube is removed at the gas machine end, and an added length of similar tubing with a flutter valve attached to its distal end is connected to it. The contents of the breathing bag are then removed by compression, whereafter the bag may or may not be removed. A flow of oxygen may or may not be continued from the gas machine, but it has been recommended that this not be used when electrocoagulation is actually being used. By the above means, room air is drawn through the expiratory port on the gas machine, ether is added to it and this mixture inhaled through the inspiratory tube. The gases eliminated by expiration are led through the double length of expiratory tubing, escaping by raising the flutter valve which has been placed at a point remote to the area where the high frequency apparatus is being employed. This flutter valve (at the end of the expiratory tubing) and the flutter valve on the inspiratory side of the gas machine prevent rebreathing, and together with the patient's respiratory efforts produce continuous movement of ether-laden air in a single patientwise direction through the apparatus. Since dead space is reduced to a minimum, there should be no carbon dioxide accumulation, and, in addition, there is no limitation to the volume of mixtures available for the patient to inspire.

While this technic is not adaptable with an apparatus where the vaporization of ether is brought about by a flow of compressed gases, it should work well on any other type of gas machine where ether is delivered into the inspiratory side of the tubing by means of an ether dropper. When resuscitation is indicated, it is necessary only to replace the bag that has been disconnected and reattach the expiratory tubing to the apparatus,

whereupon the technic is converted to a closed system.

### Regional Anesthesia

An interesting correlation between a roentgenological study of the male sacrum and caudal anesthesia has brought out several valuable factors.<sup>11</sup> The method of study followed was by making an AP view of the sacrum in routine manner, and by the use of body section radiography for the lateral view. In fifty of such studies, the apex of the hiatus of the sacral canal was determined to be at the level of the first sacral vertebral body in one instance, the second sacral in seven, the third sacral in twenty-three, the fourth sacral in thirteen, and the fifth sacral in three. Of the two cases having no sacral apex, there was one exhibiting a complete agenesis of the posterior wall, and in another individual there was found to be no sacral canal.

The majority had an anteroposterior diameter of the sacral canal hiatus of from 2 to 4 mm.; the largest was 6 mm. and the smallest 1 mm. Twelve per cent of the sacra studied were found to have no definable sacral hiatus on the lateral planigraphic film. In 14 per cent of the cases, the cornua were flat or absent. A completely blocked lumen of the canal at the opening was noted in 10 per cent of the cases, and a partial block either at the opening or above it was observed in 14 per cent. There was an exaggerated sacral curve in 16 per cent of these individuals. In conclusion, it has been shown that the significant anatomical findings contributing to unsuccessful analgesia are narrowed AP diameter, absence of hiatus, blocked lumen, and agenesis of the posterior walls of the caudal canal.

It has been a recognized practice not to inject local anesthetic drugs into traumatized or infected tissues. It has now been suggested<sup>12</sup> that penicillin could be

dissolved in the same fluid as the local anesthetic agent. Procaine or metycaine with 250 OU of penicillin did not interfere with the antibacterial properties of penicillin against *Staphylococcus aureus*, while the addition of the same number of Oxford units of penicillin sodium per cubic centimeter to procaine or metycaine solutions produced good anesthesia and relaxation for continuous caudal anesthesia in obstetrics, and for abdominal and field blocks, tonsillectomies and dental procedures, as well as for sacral block for hemorrhoidectomy.

### Intravenous Anesthesia

Now that sodium pentothal has completed its full ten years of use, it seems timely that the fundamental principles of the method which have stood the test of time, and which it is generally believed essential to its safe and satisfactory clinical use, might be reviewed.<sup>13</sup> One of the factors advantageous to intravenous anesthesia has been that the agent is injected directly into the blood stream for distribution to the central nervous system, in contradistinction to inhalation anesthesia, where many factors may prevent the agent from reaching the blood stream or being absorbed by it. In rectal or colonic anesthesia, similar possibilities occur. On the other hand, intravenous anesthesia is, strictly speaking, another type of general anesthesia and, because this is so, most of the difficulties and drawbacks associated with this type of anesthesia are inherent to it. It should be realized, too, that in order to overcome these drawbacks it is usually necessary to have available some of the equipment ordinarily considered necessary for the administration of an inhalation anesthetic agent.

It is soundly established that there is a wide discrepancy in the tolerance of patients for pentothal. This variation

occurs not only in normal, healthy individuals, but also may vary exceptionally in the same individual in both health and disease. It is now known that pentothal sodium *per se* is not any more dangerous to patients in the condition of shock than any other general anesthetic agent, but becomes dangerous only when it is given to individuals in shock according to ordinary standards and in so-called average doses.

The majority of anesthesiologists believe that pentothal sodium does not produce adequate skeletal muscle relaxation in safe concentration, particularly of those muscles of the abdominal wall. Similarly, certain other types of operations, such as those on the upper part of the respiratory tract, where problems of the airway and others occur, neutralize in a hazardous way the desirable features of pentothal sodium anesthesia.

Much work has been done regarding supplementation of pentothal, in view of the fact that it is such an excellent inducing agent. It would appear that the most significant and valuable combinations were those with local, regional, and block anesthesia, with or without oxygen, or combined with nitrous oxide and oxygen. The combination of intravenous anesthesia with spinal has many possibilities, while the use of topical anesthesia has increased the value and safety of intravenous anesthesia when employed for intraoral and laryngeal operations.

Because of the simplicity of the technique, pentothal anesthesia is becoming to be administered more and more by inexperienced individuals. Unfortunately, in this respect, anesthesiologists have little or no control. Teaching the correct administration and its dangers and limitations appears to be the only alternative.

Pentothal today is used mostly in a 2.5 per cent solution, although many

institutions still adhere to the 5 per cent solution. Equipment advocated for its use is quite varied, ranging from the simple intravenous needle and syringe, which can be maintained in position by adhesive straps, to the very complex and elaborate specimens of apparatus offered.

The use of topical anesthesia and intubation with an endotracheal catheter has increased the safety of pentothal for certain operations about the oropharynx and nasopharynx, which in the past have been viewed as unsafe practices with this agent, mainly because of the difficulty of maintenance of a patent airway and the danger of aspiration of blood, mucus, vomitus, or pus into the tracheobronchial tree with persistence of a state of hyperactivity of the pharyngolaryngeal reflexes. This combination of agents and methods becomes valuable when viewed from the standpoint of freedom from the danger of fire and explosion.

During the recent World War, pentothal has shown itself to be one of the outstanding advances in modern military surgery. This conclusion remains factual in spite of the instances where a rather high mortality rate existed as the result of faulty administration by inexperienced personnel or the selection of the method for cases in which it should not have been the method of choice.

### Fire and Explosion

While the incidence of disasters of this kind has not increased, they constitute an ever present potential source of danger in the operating rooms under certain conditions. It is necessary, in order to produce a fire or explosion in the operating room, that two conditions be present: there must be an ignitable mixture of vapors or gases, and the mixture must come in contact with a source of heat sufficient in intensity to ignite it.<sup>14</sup> The usual ignitable sub-

stances during the state of anesthesia are ethyl ether, ethylene, or cyclopropane, each or all in combination with an adequate amount of oxygen. A list of the obvious precautions given is:

1. Open flames (gas, alcohol) and glowing fires are not permissible.

2. The electrical equipment should be inspected frequently and maintained in excellent condition.

3. Containers and apparatus for the control of volatile substances and compressed gases, including oxygen and nitrous oxide, should likewise be inspected frequently and maintained in a leakless operating condition.

4. Both oxygen and nitrous oxide or their mixtures must be viewed as sources of support for combustion.

Certain specific rules for anesthetist:

1. Whenever the cautery or other potentially igniting agents must be employed near the face or the air passages, only noninflammable agents must be used.

2. Inflammable agents may be employed in the presence of cautery, etc., only if the anesthetist is experienced sufficiently to use a closed carbon dioxide absorption technic without leaks.

3. Ignition through static electricity and precautions against it have been controversial. Grounding of all objects in contact or in near proximity to the patient has been advocated, but many engineers believe that complete grounding is not absolutely possible. Possibly, from experience to date, the common practice of safeguard against static sparks is the most efficient, namely, the rule that the anesthetist maintain, in some way at all times during anesthesia, contact with the patient, apparatus and table when preparing to anesthetize a patient, and to maintain this contact between all objects within the area likely to contain ignitable mixtures throughout the administration.

## Curare

This drug was employed by South American Indians in hunting and fighting. It is obtained by brewing various portions of several species of the *Strychnos* genus. It is supplied commercially as an extract in 5 cc. rubber-stoppered ampoules, containing a 2 per cent sterile solution of a standard drug. The drug produces an interruption of nerve impulses at the myoneural junction, so that muscles will not respond to injected acetylcholine nor to stimulation of its nerve. The action is essentially peripheral, although certain central action has been suspected.

This drug is now rather ingeniously applied to anesthesiology. Usually, sensitivity to pain is brought about by means of an anesthetic agent only to the lighter planes of anesthesia, and muscular relaxation is produced by means of the intravenous injection of curare. As supplied commercially, each cubic centimeter contains 20 units. Twenty to 120 units intravenously may produce excellent relaxation of muscles. Its use is not without danger even though extremely advantageous, and it is still considered in its experimental phase. Nevertheless, for the reader who is experienced in methods of anesthesia, a moderately comprehensive list of references is included.<sup>15-25</sup>

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## ARTHRITIS AND RHEUMATOID CONDITIONS

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Relatively few important contributions to the literature bearing upon arthritis and rheumatic states in general have appeared during the past year, doubtless because of the induction of large numbers of the medical profession into the Armed Forces. However, observations on a large scale in several centers created for the study of these diseases have gone forward and are still going forward upon men in the Services affected by these conditions, and it is to be expected that data of much significance will shortly be forthcoming.

### Still's Disease

It is frequently difficult to differentiate Still's disease from tuberculosis and rheumatic heart disease, according to Ashmun.<sup>1</sup> Besides the polyarthritis, children with Still's disease frequently have enlarged lymph nodes and spleen. Swelling of the joints is periarticular and the joints most commonly involved are the fingers, wrists, knees, and cervical vertebrae. Some children acquire cardiac enlargement comparatively early in the disease, although many escape it entirely.

Because of the frequency of positive tests for undulant fever, Ashmun<sup>1</sup> believes that most cases of Still's disease are caused by brucellosis and streptococci. Consequently, a rather definite plan for treating these patients has been evolved. A careful physical examination is done first, followed by routine laboratory studies, including a patch test and a skin test for undulant fever. Then foci of infection, if present, are removed, providing the condition of the patient warrants it. Each case is then given a course consisting of 4 minims of *streptococcus immunogen* plus 4 minims of *streptococcus immunogen arthritis* at weekly intervals for a month. To this is added 1 minim of *undulant fever vaccine* at the first injection for those cases with positive skin tests. At subsequent injections this dose is raised to 2, 4, and 8 minims and then the patient is carried along on a maintenance dose of 4 minims each of the streptococcus immunogen plus 4 to 8 minims of the undulant fever vaccine, according to the individual reaction.

Besides the course of vaccines, each child is given large doses of *vitamin A*,

*B, C, and D*, and a diet containing large amounts of meat, but rather small amounts of milk.

### Acromegaly and Joint Disease

The joint changes present in acromegaly have frequently engaged the attention of students of arthritis, and there has been some speculation concerning the possible rôle of the endocrine glands in the etiology of rheumatoid arthritis. Recently, Waite, Bennett, and Bauer<sup>2</sup> had an opportunity to study in detail an acromegalic who died of bacterial endocarditis. This patient had had acromegaly for twenty years previous to this study, but had been in a comparatively quiescent state for the previous fifteen years.

It is recognized that the joint changes in degenerative joint disease may be indistinguishable from those produced by acromegaly, a fact which has probably delayed the recognition of the latter as being of a specific nature. The histologic picture of the joint changes in this case, especially where the changes were marked, closely resembled those found in nonspecific degenerative joint disease. The spine showed gross, microscopic, and radiologic changes which could be duplicated in many an elderly nonacromegalic individual, with three exceptions.

First, the hypertrophic changes at the margin of the intervertebral articulations were more marked; secondly, there was reversal of the relationship in size between the eleventh and twelfth thoracic and the first and second lumbar segments; and, finally, there was bony union between two dorsal vertebrae, along with degeneration of the intervertebral disk. None of these changes could be attributed to an infectious process, either clinically or histologically. Throughout the spine there was generalized active endochondral ossification, a process which is

entirely abnormal for an individual the age (fifty-eight years) of this one, and cannot be attributed to degenerative bone disease. It seems entirely logical to conclude that these changes may represent the result of a specific hormonal stimulation to the skeletal system resulting in new growth of bone and cartilage.

Lesions in the peripheral joints, while rather marked, still were of the same pattern as found in degenerative joint disease with the exception of one toe joint which showed changes not characteristic of degenerative disease but compatible with changes described by others in acromegaly.

### Gouty Arthritis

Gouty arthritis has appeared from time to time as a complication following major surgery. Ficarra and Adams<sup>3</sup> studied in detail five such cases in which gouty arthritis appeared suddenly within five days postoperatively. All patients were men and all were over fifty five years of age. Four of them showed hypoproteinemia but no determination was made on the other. All showed hyperuricemia of variable degree.

Low blood protein levels may be produced by an inadequate intake as in loss of appetite, vomiting, and restriction by the surgeon, or by excessive protein loss as in draining wounds, extensive burns, and long-standing albuminuria. Whatever the cause of hypoproteinemia, the result is a depleted protein reserve and also probably depleted glycogen reserve, both uniting to impair hepatic function. The rate of destruction of uric acid is therefore diminished and the blood level tends to rise. Furthermore, it seems that surgical patients excrete more protein per day at rest than during normal activity; in other words, endogenous protein metabolism is accelerated, producing an increase in blood uric acid.



Hence there is not only a diminished destruction of uric acid by the liver but also an increase in its rate of production. Still further increase in blood levels is produced if the kidney becomes involved, and the rate of excretion of uric acid is diminished. However, hyperuricemia by itself does not produce the clinical condition recognized as gouty arthritis. It seems to require a previously damaged joint, such as is produced by osteoarthritis, to provide the soil suitable for the deposition of crystals of the sodium salt of uric acid.

This complication of major surgery may be rapidly controlled by the restoration of a positive protein balance and can probably be prevented entirely by the maintenance of adequate protein intake in postoperative patients.

### Rheumatoid Spondylitis

The early diagnosis of rheumatoid spondylitis, according to Present,<sup>4</sup> is primarily a problem for the radiologist because it is only by the x-ray that the earliest pathological changes can be identified. Any of the true joints of the spine may be involved in spondylitis but the changes in the sacroiliac joints in this series of fifty patients were uniformly more advanced than those in the apophyseal or costovertebral articulations. Furthermore, the sacroiliac is more readily accessible to x-ray examination, since a simple A-P view has proved to be the most satisfactory in demonstrating early changes.

In the early stage, the inferior cartilaginous portion of the sacroiliac joint, or "pear," became mottled and lost its definition, and the lines forming its boundaries became hazy. Very little change was noted in the adjoining ilium or sacrum in this stage, but there was in some a slight increase in density about a few apophyseal joints. Early loss of

the lumbar curve was rather prominent. Later the sacroiliac joint space lost its definition completely, often showing cystic changes, and the cartilaginous portion became fragmented. There were mottling and rarefaction of the adjoining ilium and roughening of the facets of some of the apophyseal joints with narrowing of the joint spaces. Changes in the latter joints were very variable; some of them showed marked dissolution at various levels with entirely normal facets between. Calcification of the spinal ligaments began to manifest itself also in this stage. The final stage was considered to be the classical poker spine, with ankylosis of the sacroiliac and one or more apophyseal joints, calcification of various degrees of the spinal ligaments and even, in some cases, ankylosis of the diarthrodial joints of the entire spine.

Boland and Present<sup>5</sup> have hesitated to make a positive diagnosis of rheumatoid spondylitis on clinical grounds alone, although the disease may be suspected for several months before the diagnostic changes in the sacroiliac joints become discernible by x-ray. Suspicion should be aroused by the persistent complaint of stiffness and aching in the lower back, frequently with radicular pain and sciatica, in an otherwise apparently healthy young man. In this study of 100 cases of spondylitis found in soldiers,<sup>5</sup> no cases were included which did not show at least early roentgenographic changes in the sacroiliac joints.

In 18 per cent of these cases, typical rheumatoid arthritis of peripheral joints was associated with spondylitis, a fact which adds additional weight to the concept, held by many investigators, that the two are substantially the result of the same process. Furthermore, a significant number of them had involvement of the wrist, elbow, and finger joints, a

point which appears to be contradictory to the common opinion that small joints are rarely involved in spondylitis.

Of course, the etiologic agent for the disease is unknown, and in this series no constant precipitating factor could be found. There was no discernible relationship to foci of infection and the onset of symptoms was insidious in the majority, starting with complaints of low back pain and stiffness which was often worse in the morning and which disappeared during the day with moderate physical activity. There was a tendency for symptoms to disappear for a time and then return, and, as the disease progressed, pain became almost constant and was frequently described as a "dull ache." Symptoms may be mild for years and the disease may become arrested at any stage in its development, or it may go on intermittently for twenty-five years before the classical "poker back" stage is reached; or it may progress rapidly to complete rigidity of the spine within the period of a few months. It should be remembered, too, that an apparently "burned out" process which has been asymptomatic for some time may become reactivated.

In about 80 per cent of cases there was an elevation of the sedimentation rate relatively early in the disease, with a normal rate in the remaining 20 per cent. This, and the fact that constitutional reaction is usually milder than in rheumatoid arthritis of peripheral joints, should be kept in mind when confronted with a borderline case.

### **Rheumatoid Arthritis**

An attempt to find a pathological basis for some of the clinical manifestations of rheumatoid arthritis was made by Freund,<sup>6</sup> who described a nodular perineuritis in autopsy material from persons who had suffered with this dis-

ease. These nodules were found quite consistently and involved not only peripheral nerves but also such nerves as the ilioinguinal, which is not closely related to any joint. They were irregularly distributed, did not penetrate the nerve itself, and were exceedingly numerous. Their origin and significance are unknown, but it seems that they could readily account for the paresthesias and neuritic pain so common in arthritis.

While searching for similar nodules in small peripheral nerves of the amputated legs of a woman suffering with rheumatoid arthritis, inflammatory nodules scattered throughout the muscle tissue were found. These were similar to the nodules previously described in peripheral nerves, and consisted of accumulations of lymphocytes, plasma cells, and an occasional epithelial and eosinophilic cell, with few reticular fibers but an increase of collagenous connective tissue between the inflammatory cells. By way of confirmation, muscle biopsies were performed on fourteen additional living cases of rheumatoid arthritis, and in every one similar nodules were found in large numbers, along with involvement of the muscle tissue itself as manifested by areas of hydropic degeneration, edema, loss of striation, and atrophy of the fibers scattered irregularly throughout the muscles. These nerve and muscle changes appear to be the result of a widespread inflammation and are apparently of a type specific for rheumatoid arthritis. Control biopsies and autopsy material from nonarthritic subjects failed to reveal similar nodules or muscle degeneration. They may account for the neuritic and muscle pain of which these patients complain.

The great variation in the mode of onset and clinical course of rheumatoid arthritis was emphasized by Ropes and

Bauer<sup>7</sup> in an analysis of a number of illustrative cases. Symptoms of vague aching pains, loss of appetite and weight, fatigability, and numbness may precede the actual onset of joint manifestations by several months. Once the joints are affected, the tendency, in severe cases, is toward a progression of pain, swelling, limitation of motion, and deformity. Symptoms other than joint involvement are prominent, such as cold, moist hands and feet, paresthesias, anemia, subcutaneous nodules, iritis, pericarditis, and myocarditis, with atrophy of skin and muscles in the extremely severe cases. Characteristically, the disease tends to proceed in a series of exacerbations and remissions of variable length, sometimes lasting for several years. The great variation in mode of onset frequently produces considerable difficulty in making an early diagnosis, and the variability in the course of the disease makes prognosis hazardous and the evaluation of treatment inaccurate.

One case, that of a patient whose past history was of repeated infections and several surgical experiences, developed prodromal symptoms of easy fatigability and numbness of the hands for three or four months before the onset of joint symptoms. During the course of her arthritis, each remission was precipitated by a period of emotional stress, or by overwork, or by a respiratory infection. It is of interest to note that the sedimentation rate of this patient pretty accurately paralleled the clinical course of her disease in the early stages, but later became relatively fixed at a moderately elevated level despite the ups and downs of the disease.

Rheumatoid arthritis may simulate infectious arthritis with a rather abrupt onset characterized by high fever and migrating joint pain, finally localizing in a few joints. This was illustrated by

a patient who for eight weeks had a spiking temperature up to 104° and 105° F., along with involvement of several joints. There were patchy erythematous areas on the skin and a small pleural effusion was present. This patient made a relatively good recovery but subsequently had several exacerbations following periods of emotional stress or after respiratory infections.

In another patient, the abrupt onset with involvement of only one joint also suggested infectious arthritis. However, the subsequent course with involvement of other joints demonstrated the true nature of the disease. The sedimentation rate in this patient, in contrast to the first one, pretty accurately reflected the clinical course of the disease throughout. Except for two exacerbations precipitated by overwork, this patient has been in remission for six years.

Rheumatic fever may readily be simulated by rheumatoid arthritis when migratory joint symptoms and fever are accompanied by evidence of myocarditis and pericarditis as they were in the case of an eight-year-old girl who developed her first symptoms following a severe sore throat. However, the chronic course of the joint involvement over a three-year period, with deformities characteristic of rheumatoid arthritis and x-ray evidence of decalcification, made it evident that the disease was not rheumatic fever. This patient has been in remission for three years without any evidence of cardiac disease and with a slight limitation of motion in the wrists and a slight recession of the jaw as the only deformities.

It is not uncommon for trauma apparently to precipitate the initial attack of rheumatoid arthritis. When the joint involvement is monoarticular, the diagnosis is apt to be confused. However, one should hesitate to make a diagnosis

of traumatic arthritis if the joint symptoms do not appear within twelve hours of the injury and if they persist for several months. In this patient there was a minor twisting injury to the knee joint, producing stiffness and swelling which gradually disappeared. However, eight months later, without any additional trauma, symptoms returned in the same knee joint so that a diagnosis of internal derangement of the knee was made and the patient operated upon. Evidence of chronic synovitis was found by microscopic examination of tissue removed at operation, and the synovial fluid was found to have a high polymorphonuclear count and a low sugar level, findings which are inconsistent with a diagnosis of traumatic arthritis. Within four months following operation, this patient was the victim of a generalized attack of rheumatoid arthritis involving many joints.

The initial symptoms of rheumatoid arthritis may be confined to the back and lead to a diagnosis of ruptured intervertebral disk. Such was the case in a patient whose complaints were low back pain radiating to the buttock and leg, attributed by the patient to a twisting injury. At operation, no evidence of ruptured disk could be found. Following the operation, the patient was improved for a short time, but was readmitted to the hospital two months later with involvement of additional areas. At this admission, a history of previous attacks of joint pain was elicited; there was x-ray evidence of rheumatic disease of the right sacroiliac joint and the sedimentation rate was elevated.

There are probably many individuals labeled psychoneurotics who are in reality cases of early rheumatoid arthritis without any objective evidence of disease and frequently with no significant laboratory findings. This was illustrated by a young girl who had received many

forms of treatment, including psychotherapy, over a period of three years, because of her complaint of persistent backache and pain in both hips. At the end of this period, a considerable restriction of motion in her back, x-ray evidence of involvement of the sacroiliac joints, and an elevated sedimentation rate, obviously pointed to a diagnosis of rheumatoid spondylitis.

Occasionally the onset of rheumatoid arthritis consists of recurrent attacks of pain, swelling, and redness of joints, which may last two to four weeks and disappear completely, only to recur at a later date. This process may continue for three or four years, as in the case cited, with a gradual increase in the frequency and severity of each succeeding attack until the patient has a full blown case of rheumatoid arthritis.

It is probable that most patients with so-called "fibrositis" have, in reality, mild cases of rheumatoid arthritis. There may be complaints of muscle soreness and stiffness sufficiently severe to cause the patient a moderate amount of discomfort for many years before constitutional symptoms appear and joints are attacked. In the case cited, myositis existed for twenty-eight years before joint and constitutional symptoms became sufficiently prominent to make a diagnosis of rheumatoid arthritis. On the other hand, progression from myositis to rheumatoid arthritis may take place in a few months.

It is generally conceded, according to Ropes and Bauer,<sup>7</sup> that adequate treatment of rheumatoid arthritis includes **bed rest, reduction of emotional tension, exercise** to restore or maintain muscle and joint function, proper **support** for joints to allow reduction of spasm and pain and prevent deformities, **application of heat**, use of **analgesics**, an adequate **diet** with additional vita

mins and blood transfusions when indicated. Furthermore, the treatment of this or any other chronic disease requires more consideration of the patient as a human being than does a disease of shorter duration. More attention must be paid to the economic and emotional problems contributing to the production of the disease as well as those resulting from it. Finally, the patient must understand the importance of all parts of the regimen, and must see how the present treatment fits in with what has gone before and what is to follow.

Collins<sup>8</sup> feels that, while no panacea has been discovered, there nevertheless has been a definite advance in the proper management of the chronic arthritic patient as a result of experience gained during the war. The more important lesson has been the appreciation of the desirability and, in the Service, the ready availability of specialist service for each individual patient. Of slightly less value is the escape from empiricism which has resulted from newer forms of chemotherapy, progress in institutional care and social aftercare, and newer knowledge of physiological function of muscles, nerves, and joints. Intelligent treatment of the arthritic demands the deepest knowledge of the etiology in each individual and the closest cooperation between the internist, the orthopedist, and the psychiatrist.

According to Pemberton<sup>9</sup> the pendulum of thought on the relationship of focal infection to arthritis is swinging from overemphasis, with its many disappointments, to skepticism or even to complete discard in some quarters. The welfare of the arthritic demands an intelligent evaluation of the problem, but infection, focal or otherwise, should never be accepted as the basic cause of the many deviations of physiology encountered in arthritis. Minor changes apparently dis-

turb the normal physiologic relationship between the great systems involved, especially the neuroendocrine, vascular, hemapoietic, and gastrointestinal, so that frequently no one single defect is predominant.

There is increasing clinical and experimental evidence to indicate that dysfunction of the endocrine system has some etiologic relationship to the two common types of arthritis, atrophic and hypertrophic. It seems highly probable that multiple deficiencies, or even hypofunction and hyperfunction, of different elements in the chain may exist simultaneously in the same individual. Endocrine therapy up to now has been mainly replacement and has been confined, to a large extent, to the treatment of "arthritis of the menopause," with gratifying results in a high percentage of instances. However, hypertrophic arthritis, which is the pathological type of "arthritis of the menopause," is amenable to a program of conditioned rest without resorting to "specific" therapy. It should not be inferred, however, that specific therapy should be withheld if indicated and if available, but that it should be coordinated into a broader program of management with the ultimate view of establishing physiologic equilibrium.

Effective therapy of arthritis requires a program which on the one hand removes so far as possible such accessible factors as worry, fatigue, faulty body mechanics, poor nutrition and focal infection, and on the other hand attempts to provide rest, correction of anemia, endocrine replacement, correction of gastrointestinal dysfunction, tonic medication, sedation, physical therapy, and optimum nutrition. Bed rest, combined with mild sedation, which is often entirely neglected or inadequately applied, is absolutely essential to the successful management of the sick arthritic. Arrest of the arthritic

process is frequently amenable to the application of physiologic principles which may appear too simple and obvious to merit attention.

Since most specific joint infections respond well to chemotherapy, this diagnosis must be kept in mind whenever the joint lesion appears to be inflammatory. The diagnosis in suspected cases should be made by the isolation of the micro-organism from the blood or from a highly cellular joint fluid. Suppurative arthritis, which is usually monoarticular, is primarily an orthopedic problem, and the prognosis with *penicillin* treatment is excellent. Gonococcal arthritis, which has a predilection for the knees and feet, is frequently polyarticular and may not become evident for a month or more following the venereal infection. The diagnosis should be suspected where there is a recent history of gonorrhea, and can be confirmed later by the complement fixation test. It is extremely important that the *sulfonamides* or *penicillin* be started early in this disease because of the extensive joint destruction which takes place in untreated cases, and the joint must be at complete rest while specific treatment is being given.

Frequently undulant fever is accompanied by arthritis of large joints, a fact which should be remembered when confronted by a patient with arthritis and a relapsing fever. Treatment, unfortunately, is not altogether satisfactory but the sulfonamides should be tried.

Collins<sup>8</sup> believes that adequate rest is the keynote to the successful management of rheumatoid arthritis and that absolute bed rest is mandatory in the acute stage, along with splinting of affected joints. Splints may be left on for a week or so and then removed and the joint put passively through its range of painless motion once or twice daily.

Weight-bearing is to be avoided until active inflammation has subsided. Analgesics, such as salicylates, should be used freely, especially at night to assist in obtaining rest. The diet should be well balanced with normal vitamin intake. Local heat is of benefit and daily treatment at home by simple methods is better than treatment with more elaborate equipment which requires the patient to travel a long distance. Elimination of focal infection is advisable on the ground that there is less for the patient's resistance to battle, but a close etiological relationship between focal infection and arthritis is not definitely proved. Patients should obviously never be told that the removal of an infected tooth will cure their arthritis.

Aside from the commonly recognized types of fibrositis, such as toxic, mechanical, and postural, that due to psychogenic disorders is deserving of attention. This form is far more common than is usually suspected, is often characterized by vague shifting pain, and is frequently accompanied by manifestations of an underlying emotional disorder. Successful treatment must, of course, be directed to the emotional disorder.

**X-ray Treatment**—A great deal of the recent literature on the x-ray treatment of the arthritides has been summarized by Kaplan.<sup>9</sup> Benefit has been obtained in both rheumatoid arthritis and in spondylitis, particularly in those cases in which treatment is begun early. However, it is not entirely clear whether the course of the disease is actually interrupted or whether benefits are entirely symptomatic. It appears, especially in spondylitis, that sometimes the course of the disease is actually arrested.

Radon ointment was tried, although the penetrating power of this form of radium was known to be very slight. This form of treatment, according to

Kaplan,<sup>9</sup> was entirely without effect in the treatment of arthritic conditions.

High voltage x-ray therapy may rapidly relieve the pain of bursitis and over a period of time frequently induces resolution of the calcific deposits in the bursa. In the treatment of bursitis, Kaplan<sup>9</sup> recommends high voltage x-ray given through several areas at each sitting, two or three times per week in acute cases, and one or two times in the chronic cases. Treatment should continue for six to eight weeks, but relief from pain is usually attained in four to five treatments. With proper precautions, no ill effects have been noted.

**Vasodilatation**—Heat has long been accepted in the treatment of rheumatoid arthritis because of its ability to produce capillary dilatation with resultant increase in blood supply to affected parts. It occurred to Kurtz, Orth, and Sepulveda<sup>10</sup> that generalized vasodilatation produced by means other than heat might also be of benefit. *Nicotinic acid* was chosen as the vasodilating agent and thirty-six patients who had had active rheumatoid arthritis for from four months to thirty years were treated. Of the thirty-six, twenty-eight were bed patients, five of whom were so ill that they were unable to walk even with the aid of crutches. Five patients had had the disease for less than a year, five for less than two years, and the remaining twenty-six for longer periods of time.

Inpatients were treated with an initial dose of 200 cc. of an 0.05 per cent solution of nicotinic acid in normal saline given intravenously over a period of one to three hours. If this dose was well tolerated, it was increased to 400 cc. of the 0.05 per cent solution, which was usually sufficient to produce a visible blush of the skin and a subjective sensation of warmth. This was repeated daily while the patient was under treatment. Occa-

sionally, this was insufficient to produce the desired vascular dilatation and a few patients apparently developed a tolerance to the drug. In that case, the dose was increased by giving a 0.1 per cent solution. Besides the daily intravenous dose, the drug was also administered by mouth twice daily on an empty stomach, in doses of 50 mg. every fifteen minutes for three doses. If this proved insufficient to produce a flush lasting an hour, the dose was increased to 100 or 200 mg. for each dose every fifteen minutes. In one case the dose had to be increased to 600 mg. every fifteen minutes. It can readily be seen that there was considerable variation from individual to individual in the amounts required to produce adequate flushing of the skin. Consequently, a separate dosage schedule had to be figured out for each individual until the minimum amount required to produce a flush for one hour was determined. Patients treated in the outpatient department were given three oral doses every day, except for three days per week on each of which they were given two oral doses and one intravenous dose. This treatment was continued as long as any improvement was noted, some patients having taken it daily for eleven months. Only one patient reacted allergically to nicotinic acid and had to discontinue treatment.

Results were determined subjectively and objectively by goniometric measurements of the range of motion in diseased joints. Subjectively, twenty-five patients were improved and, objectively, twenty-six were improved. There were no significant changes in the sedimentation rates of any of these patients.

Most of the hospitalized patients were given *physiotherapy* also during their course of treatment. However, three of the outpatients who obtained considerable benefit had no physiotherapy at all

and fifteen of the hospitalized patients had previous hospital admissions for physical therapy without obtaining the benefit they did from this admission.

These results may be regarded as preliminary, because the longest period of observation has been only thirteen months.

**Penicillin**—Inevitably, in the search for a suitable therapeutic agent for the treatment of rheumatoid arthritis, penicillin comes in for its share of attention. Comroe<sup>11</sup> treated six rheumatoid arthritides with penicillin given intramuscularly at three-hour intervals in doses ranging from 100,000 to 200,000 units per twenty-four hours. This dosage was maintained for four weeks in three patients, three weeks in two patients, and two weeks in one patient.

Of these six patients, five had had rheumatoid arthritis for at least four years, while the other one had the first manifestation of the disease only eight months prior to the institution of treatment. In none of these patients was there any evidence of improvement, either subjectively or objectively.

### Osteoarthritis

It is the opinion of Hendry<sup>12</sup> that the treatment of osteoarthritis is primarily a mechanical problem and comes logically within the province of the orthopedic surgeon. It is a degenerative disease and afflicts the elderly most commonly, although young individuals with joints damaged by trauma or disease may also be afflicted. It is not uncommon in young persons who subject their joints to a great deal of stress or misuse, or those in certain laboring occupations, or those who walk in high-heeled shoes. It is found in occupations requiring excessive use of one set of muscles wherein the opposing set is allowed to atrophy, producing faulty posture and unequal stress on joints.

As a preventive measure, congenital orthopedic deformities should be corrected early in childhood, fractures should be reduced so as to maintain the normal joint axis, and obese individuals should be persuaded to reduce their weight to reasonable levels.

In the treatment of osteoarthritis, Hendry<sup>12</sup> believes that gentle manipulation of joints in which there is restriction of movement with minimal arthritic changes is of benefit, but should never be used in the elderly patient. Rest and external fixation of an osteoarthritic joint will do much to relieve pain and lessen muscle spasm. Fixation can be accomplished by plaster splints, or, if it is desirable to maintain fixation over a longer period of time, by semipermanent fixed braces. Arthrodesis, however, must be used with caution, especially in the elderly, because the additional burden placed on functionally related joints may be sufficient to induce osteoarthritis in them. The fallacy so prevalent, especially among the laity, that arthritic joints must be kept moving, should be actively opposed.

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## CANCER

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During the past year there has been a continued limitation of the work in cancer research because of the war and its consequent displacement of scientific workers, but even under the inevitable handicaps, much worthwhile experimentation has been done. One notices slightly different trends predominating for periods of time so that the weight of research effort shifts, not like waves and troughs, but rather like a blending change in a spectrum so that brighter concentrations of endeavor make certain fields at different times more evident to the observer. This does not mean that concentrated effort makes one field of research shine at the expense of others, but rather that the whole spectrum is becoming brighter by individually varying increases.

For the past several years attention has been drawn particularly to the milk factor in mouse tumor production and to the study of endocrine effects in tumor incidence and metabolism. The development and study of these factors still play a large part in the overall picture of cancer research, but at the present moment there is particular emphasis on the dietary effects on tumors and tumor production. In addition to the dietary factor, a large amount of effort is being directed toward the chemotherapy of tumors.

**Diet**—Simple caloric restriction has been studied rather extensively with regard to its effect on cancer incidence in mice. Huseby, Ball, and Visscher<sup>1</sup> have investigated this problem in relationship to the incidence of mammary cancers

and other phenomena in C3H mice. They were able to remarkably reduce the incidence of this type of cancer by restricting the caloric intake one third. After weaning these virgin mice, they were maintained on a diet supplying the same amounts of protein, vitamins, and salts as the control group fed *ad libitum*. The incidence of cancer in the test group was 0 per cent as compared with 72 per cent for the control animals. These authors mention, and it seems very significant, that the ovaries, uteri, and mammae of the restricted animals showed a histologic picture compatible with pseudohypophysectomy due to inanition. They suggest that the mechanism by which the caloric restriction reduces the tumor incidence is through a secondary factor of pituitary insufficiency. They further suggest that this insufficiency acts by producing a lowered level of ovarian secretion and a relative refractoriness of the breast tissue to estrogenic substances. White and his co-workers<sup>2</sup> also studied the effect of caloric restriction on mammary tumor formation by a somewhat different approach. They noted that a 50 per cent reduction in calories without alteration in dietary essentials changed the incidence of mammary gland tumors from 100 per cent in controls to 12.5 per cent and 18.2 per cent in C3H virgin and breeding female mice respectively. They also mention that the virgin females showed no evidence of estrus. In another experiment, they painted DBA mice with methyl cholanthrene and reduced the caloric intake similarly, with the result that the development of leu-

kemia was reduced from 96.2 per cent to 35 per cent and at the same time the latent period in the development of the disease was extended over three times the usual period. The effect of dietary restriction on the estrus cycle was not mentioned in these latter animals.

For quite a few years the relationship of diet to tumor production and growth has been studied by Albert Tannenbaum, and his work has continued with an ever-increasing fund of factual evidence supporting the idea that dietary factors play a large part in tumor metabolism. He has recently noted the dependence of tumor formation on the degree of caloric restriction as well as its type.<sup>3,4</sup> He specifically studied the effect of graded carbohydrate intake as related to the formation of spontaneous mammary and induced skin tumors in the mouse. He also noted, not only the incidence of tumors, but the average time of appearance. He concluded that the lower the caloric intake, the greater the tumor inhibition and, in the case of the induced skin tumors, there was a definitely progressive increase in the latent period or time of appearance as the caloric restriction was increased. His other experiments dealing with the composition of the diet seem to show quite definitely that on a specific caloric restriction a high fat diet is less effective as an inhibitory agent than a diet with a low fat content. He suggests that the evidence presented means that the increased effect on tumor formation of a high fat diet is due to some specific action of fat. It is rather surprising that no particular mention is made of the possible effect of these diets on the endocrine systems. It would certainly be interesting to know if the ovaries were changed by these diets and, if such a change existed, what relation the degree of change might have

had to the quantitative and qualitative dietary differences.

Connell<sup>5</sup> studied the effect of protein intake in mouse cancer. The test animals used were mice bearing sarcoma transplants and the rate of tumor growth was judged by a measurement of tumor expansion. The control animals were on a maintenance diet and the test animals were given an adequate caloric intake but a restricted protein level. The tumor growth in the control animals was more than double that observed in the test animals. Another rather surprising observation in these experiments was that the control animals did not maintain as good a general condition as did the test animals on the restricted protein diets. The latter were much more active throughout the experiment. There were five spontaneous recoveries in the test animals as compared with only one among the controls. Here again there is no specific mention of any secondary effect on the endocrine organs, but the author concludes that there is apparently a distinct inhibition in the growth of this type of mouse sarcoma resulting from a selective restriction of protein in a diet of adequate caloric value.

A more specific dietary element as a factor in mammary tumor formation in C3H mice was studied by White and White.<sup>6</sup> A low lysine diet was fed these animals and the result of this and previous experiments showed a lowered incidence of spontaneous tumors. These authors again mention that on this diet estrus was suppressed and they remark that this suppression may be a very important, if not the most important, factor, in the lowered incidence of spontaneous mammary tumors. Koehler<sup>7</sup> studied this same problem and noted that there was some inhibition of mammary tumor growth in its early stages, but more rapid growth

in the later stages. He also studied the effect of a lysine-deficient diet in two human subjects and found that they maintained their nitrogen balance.

White<sup>8</sup> also studied the effect of diet on the development of the mammary glands in C3H mice and found that there was no growth of mammary tissue in virgin females when the diet was low in cystine from the time of weaning. A low caloric diet produced little mammary growth and a low lysine diet produced an inconstant inhibition of growth. He noted that if estrus was maintained in these animals by stilbestrol, then the mammary tissue continued to grow despite a low cystine diet. These observations by White relative to the coincidental, or possibly primary, effect on estrus seem very important in the entire study of the dietary factor, and it certainly is almost imperative that any further work on this factor should be accompanied by information concerning the estrus state.

A very interesting and significant experimental study on the source of tumor proteins has been done by White and Belkin.<sup>9</sup> They call attention to the fact that in growing animals the only source of newly deposited nitrogenous material is the dietary protein, but the growth of a tumor may use as its source of protein either of the funds of supply; namely, dietary protein or tissue protein of the host. The object of the experiment was to determine which of these sources was used by transplanted tumors in young mice. A control group of mice was fed an adequate diet and a similar test group was held on a low nitrogen diet containing no protein. After reasonable adaptation to these diets, tumor transplants were made and the rate of tumor growth noted. To quote the authors, "There was no apparent difference in the number of successful tumor transplants between the two groups of

mice or in the time of appearance of the earliest palpable lump. These are really astonishing observations in view of the differences in diet. The low-nitrogen-diet group received in their food at best only the meager amount of incomplete protein fragments contained in one of the vitamin supplements. They were in negative nitrogen balance at all times and lost a quarter of their body weight during the three weeks. Nevertheless, this lack of dietary protein resulted in no apparent interference in the establishment of the tumor transplant. There was, however, a statistically significant alteration in the growth rate of the tumors." The transplanted tumors in those mice getting no protein grew at approximately 74 per cent of the rate of those in control mice and during the period of growth the negative nitrogen balance showed that the need for protein was greater than that supplied by the diet. The authors conclude that a tumor can draw upon the host's tissue protein to supply its metabolic needs. A complementary study by White,<sup>10</sup> in which the nitrogen balance was investigated, shows that under the conditions of stress created in the experiment the tumor can use the host as a source of nitrogenous nutrition.

It must be kept in mind that these fascinating studies dealing with dietary effects on tumor production and metabolism in animals cannot be immediately applied to the human tumor problems. Some writers have advocated definite changes in the human dietary regime and base their ideas on experimentations similar to those described above, but it is well to remember that some of these severe restrictions in diet, although feasible in experimental animals, are not compatible with healthful human life. Further study may make some of these ideas come within reason, but at the

present time they must be considered simply for their value in the study of animal tumor production and metabolism.

**Milk Factor**—For a number of years a very concentrated study has been made on the mouse mammary tumor agent or milk factor discovered to play a large part in the production of breast tumors in mice. It seems hardly necessary to completely review this subject for it has been extensively treated in many of the research journals and other publications including the previous volumes of *The Cyclopedia of Medicine, Surgery, and Specialties*. A few additional studies might well be mentioned because of their interest in the further development of our knowledge concerning this factor. Heston, Deringer, and Andervont<sup>11</sup> have evaluated the gene-milk agent relationship in mammary tumor development and they find that heredity plays quite a part in both the production and the effect of the milk factor. They state that the genetic constitution of a mouse has an influence in its ability to propagate and transmit the milk-agent. Their experiments suggest that there are at least two sets of genetic factors influencing breast tumor development. One set determines the susceptibility of a mammary-tissue cell to the hormonal and milk-agent stimuli and the other determines the propagation of the milk-agent. It is well to keep these two genetic influences in mind whenever there are studies made on mouse mammary tumors, whether they occur spontaneously or through hormonal experimentation. Dmochowski<sup>12</sup> has discovered some interesting facts in relationship to age and dosage in the induction of breast cancer in mice by the mouse mammary tumor agent. Using mice in which the mammary glands had already completed their development in the absence of the milk-agent, he was able to produce a high

incidence of breast cancer by giving the milk-agent. This is in contrast to the induction of such tumors by estrogenic substances. The latter can induce mammary cancers in susceptible mice only if the development of the mammary glands has taken place in the presence of the mammary tumor agent. Older mice were found to require much larger quantities of mammary tumor agent than did young mice in order to induce the same number of tumors. This work suggests that estrogenic substances need the milk factor as a conditioner in order that tumors may be produced in fully developed glands. It also means that older breast tissue offers some resistance to the influence of the mammary tumor agent.

Many other studies on the milk agent suggest its relationship to a virus or viruslike entity. This similarity has previously been pointed out, but Andervont and Bryan<sup>13</sup> have further enhanced the idea. They noticed that the tumor-producing agent was inactivated when held at 140° or 150° F. for thirty minutes. The same observation held for mammary tumor extracts at 130° or 150° F. The agent was found to be stable at low temperatures, but the whole tumors lost their activity after eighty days in a 50 per cent saline-glycerine solution at 46° F. They found that the active principle could pass through a Berkefeld filter and that certain tumor extracts produced neutralizing antibodies when injected intraperitoneally into rabbits. These antibodies had the ability to neutralize the agent both *in vitro* and *in vivo*. Bittner, Evans, and Green<sup>14</sup> recovered the mammary milk-agent from a transplanted breast carcinoma that was carried through ten passages in mice that originally did not have the agent. This suggests that the agent can go on almost indefinitely in growing tumor tissue, at least *in vivo*. It would be interesting

to know if the agent still goes on when the mammary tumor tissue is grown in tissue culture, for these authors suggest that the agent may be responsible for the genetic mutations found in transplantable tumors. They also found that the agent could be recovered from the yolk sac of chick embryos twelve days after implantation into eggs of either tumor suspensions of cell-free filtrates or tissue harboring the active agent. Some of this material on the nature and propensities of the milk tumor agent is difficult to orientate so that the element of heredity and the viruslike properties can be dovetailed. In all likelihood our confusion might be immeasurably eradicated by an exact knowledge of what constitutes a virus. As yet there has been no distinct tie-up found between the tumor agent as found in mice and the possibility of such an agent influencing human breast cancers. The possibility of such an agent in the human is real enough to suggest that women in families with a history of breast cancer should probably avoid breast feeding of their infants, particularly the female infants. There will, no doubt, be some opportunity in the future to seek such an agent in the milk of recently delivered mothers having carcinoma of the breast.

**Heredity**—Innumerable studies have been done in the past on the influence of heredity in tumor production and these studies are continuing unabated. Some studies are now being made on a large scale with human clinical material, but the great difficulties involved in human genetics make immediate answers practically impossible. Of the many experiments done on animals to elucidate this problem, one of the more recent by Burack *et al.*<sup>15</sup> is interesting because of the type of tumor involved in the study. These authors have demonstrated a greatly increased frequency of benign

mammary fibroadenomata incidence due to close inbreeding in the Albany strain of rats. Since many pathologists think that this type of lesion is due to an endocrine disturbance rather than a true neoplastic change, it is of importance that inbreeding had such an influence. No mention is made in this study of the part that might have been played by a milk factor similar to that found in mice.

**Lymphocytes**—Many investigators and observers have suggested that the lymphocytes may play a part in the body's defense mechanism against neoplasms of any sort. Recently, however, Kelsall<sup>16</sup> has taken an opposite view from these suggestions of the past. The author points out many facts that have previously been observed, but interprets them differently. The idea that the lymphocyte might contribute to the growth of tumors or possibly even instigate them grew out of the observation that there was a direct correlation between the amount of lymphoid tissue in the intestine and the incidence of spontaneous mammary tumors in several pure strains of mice. The idea is further elaborated by the fact that mammary tumors often have many lymphocytes present and that such tumors most frequently metastasize to lymph nodes, but even the other metastatic foci have lymphocytes present. The mammary tumor inciter in mice is found in milk, blood, spleen, thymus, lactating mammary tissue, and breast tumors of strains high in spontaneous tumor incidence. No cell is as numerous in these fluids and organs as is the lymphocyte. It is also pointed out that the milk factor is concentrated in milk sediment after centrifuging and so are the lymphocytes. It might be well to insert a note of warning at this point in the author's evidence. As seen in previous work reviewed here, the milk factor passes through a Berkefeld filter

and is also present in cell-free extracts. Further evidence, however, is offered by the observation that more mammary tumors are found in breeding mice than in virgins, and one prominent histological change in the mammary gland during pregnancy and lactation is the presence of quantities of lymphocytes. Other relationships of the possible tumor-lymphocyte connection are mentioned, such as the production of tissue and blood lymphocytosis in chronic irritation, some endocrine imbalances, oral syphilis, and lymphoblastic tissue stimulation by unbalanced sex hormones. On the opposite side of the picture the author mentions that chronic inanition decreases both lymphocytes and tumors, as also does radiation. In regard to the lymphocyte itself, it is mentioned that the nucleus of this cell is the largest in proportion to the cytoplasm of all cells, and that this nucleus contains larger nucleoli and more nucleic acid than most cells. These facts are offered with the notation that nucleoprotein disturbance is often mentioned as a basis for an intracellular cause of neoplasia, so that it is suggested that the lymphocyte may modify nucleoproteins. Although Kelsall takes, or offers, this viewpoint about the possible etiological relationship of lymphocytes to tumor production, there seems relatively little reason at present to follow this idea. It is rather new and different, but this does not make it necessarily tenable, although it must be given consideration. There are many evidences against such an idea, and the mere presence of lymphocytes in and around tumors does not mean that they should be considered as instigators. It would have been just as wise for observers to have stated that the lymphocyte was the cause of syphilis in the days before the discovery of the real cause. As a matter of fact, it might be just as logical to say

that the antibody present in any disease was the cause of the disease, particularly if the antigen is unknown.

Some very interesting studies have recently been made on the lymphocytes and that by Dougherty, White, and Chase<sup>17</sup> concerning the relationship of the antibody content of normal and malignant lymphocytes is particularly notable. These authors have previously demonstrated the presence of antibodies in normal lymphocytes,<sup>18</sup> and more recently a similar and beautiful piece of work has been done by Harris, Grimm, Mertens, and Ehrlich.<sup>19</sup> The question investigated by the original authors was whether lymphocytes in lymphosarcoma also contained antibody. They found that tumor cells had a slightly higher antibody content than did normal cells, and that tumor cells were capable of obtaining antibody from some other source in the body, presumably normal lymphocytes. There was a reversible exchange of antibody protein between normal and malignant lymphocytes.

**Carcinogenesis** - Since the discovery of carcinogens many years ago, the study of them and the tumors resulting from them has been constant. Much of our present knowledge of the natural history of tumors has been learned from the use of these substances. Recently Pizzolato and Beard<sup>20</sup> have studied the effect of irradiation on some agents suspected of having carcinogenic qualities and their conclusion was that sterols and related substances when irradiated show more carcinogenic activity than before irradiation. In their work they used a colony of rats in which no spontaneous tumors had arisen during the past seventeen years. Using irradiated and nonirradiated cholesterol, ergosterol, desoxycholic acid, and dehydrodesoxycholic acid, bile salts, and human gallstones, they found that no tumors arose in 385 rats during

eighteen months of injection of doses from 10 to 100 mg. Four tumors, however, were produced in four animals after injection of the following substances: A fibrosarcoma from irradiated cholesterol; two anaplastic sarcomas, one each from cholesterol and from irradiated dehydrodesoxycholic acid and a keratinizing squamous cell carcinoma from irradiated ergosterol. The authors believe that the production of these four tumors is of some significance. This is certainly true when it is realized that no spontaneous tumors have occurred in this rat colony, but the percentage of tumor production is so small that perhaps the significance is not too great. It is of importance, however, to study more of the naturally occurring sterols and related substances for by so doing we are more apt to arrive at a knowledge of some of the body substances related to spontaneously occurring tumors. Mottram,<sup>21</sup> in studying the change from benign to malignant in chemically induced warts in mice, states that he thinks the change produced by painting with carcinogenic substances is due to the initiation of new localized malignant changes within the warts. The gradual change from benign to malignant is thought to represent the gradual replacement of slow-growing benign by fast-growing malignant cells, rather than a simple stepup process. The more proliferative cells are more sensitive to the carcinogen and as a result repeated paintings cause the change in more and more of these sensitive cells. This seems to suggest that the effect of repeated paintings is not a cumulative one, but rather a selective process after sensitization.

Cowdry,<sup>22</sup> in a general review of consideration of precancerous lesions, states that "The designation 'precancerous lesion' is applied to a type of structural

change in a tissue in which clinical experience shows that the cells are more likely to become malignant than in other kinds of lesions." He further states, "When the fate of many individual lesions belonging to a simple type is followed, it usually happens that the malignant transformation only takes place in but a few of them. The majority of the individual lesions are not in fact precancerous. The adjective 'precancerous' relates to the type, not to the particular lesion. Perhaps two sorts of lesions are grouped under a single type, or they are all of one kind and some happen to be exposed to a carcinogen not acting on the majority." Cowdry feels that a new chemical equilibrium results when a tissue becomes malignant and it is a study of this changed equilibrium that is of such great importance. Quantitative studies are made to discover whether certain properties of epidermis increase, decrease, or remain constant in squamous cell carcinoma of inbred strain mice treated with a chemically pure carcinogen. It is found that the new equilibrium is characterized by decreases from the normal in calcium, iron, and lipid, while sodium, potassium, magnesium, and ascorbic acid show no noteworthy changes. Decreases have been found by others in cholesterol, copper, zinc, and in biotin. Cowdry has noticed that the new equilibrium is established within less than ten days and is maintained for several weeks until a transformation is seen in at least a few cells. This new equilibrium is also characterized by larger cells with greater volume increase in cytoplasm than in nucleus so that the nucleocytoplasmic ratio is decreased. Ribonucleic acid increases in the cytoplasm, the chromosomes enlarge, and the rate of mitosis increases progressively. Other intracellular changes occur which suggest a fundamental increase

in intranuclear viscosity. It is unknown just where and when this transformation occurs, but all these studies, and we hope those of the future, are greatly increasing the factual knowledge of that strange time and place where malignancy is born.

#### Characteristics of Tumor Tissues

—One seemingly very important study on the inhibition of carcinogenic action has been made by Lacassagne, Bui-Hoi, and Rudali.<sup>23</sup> These authors started with the idea that the mutation which transforms a normal cell into a malignant cell results from the alteration of an organic substrate by the fixation to it of some toxic molecules. This idea, of course, is not new, and there have been some suggestions previously of the ideas at which they arrived. They used two carcinogenic hydrocarbon compounds, one having little or no toxicity, and the other being quite potent. Both compounds resembled each other as closely as possible in molecular structure. Their purpose was to determine whether the fixation of the slightly toxic compound would protect an animal to some extent against cancerization that might result from the use of the very toxic substance. It was found that certain weakly toxic hydrocarbons did act in competition with a certain highly toxic hydrocarbon on tissues of the mouse and as a result reduced the effect of the latter and delayed cancerization. In trying to explain the phenomena, the authors felt that the mechanism must be sought in an intracellular process of a physicochemical nature. They state, "It is supposed that two substances, having the same affinity because of their analogy of structure, penetrate into the same cells, where they are fixed in the same substrate. Each weakly toxic molecule, by fixing itself, would hinder by its presence the fixation of a molecule of the more toxic sub-

stance, and thus delay the appearance of certain specific lesions of the cell, amongst which figures malignant transformation." The demonstration of this blocking effect is of great significance and it remains for these men and others to use noncarcinogenic agents of similar structure to determine whether the physicochemical structure alone can produce the same blocking reaction. It is even conceivable that the body might have its own controlling or blocking substances which protect the organism against naturally occurring carcinogens.

Another study having to do with induced resistance to tumors was made by Goldfeder.<sup>24</sup> Using an inbred line of rats which were 100 per cent susceptible to a reticulum cell lymphosarcoma arising spontaneously, the author found that he could in a large percentage of cases render the animals resistant to the tumor. His method consisted of implanting tumor grafts which were previously attenuated with specific doses of x rays. In most of the animals, resistance followed the inoculation without the appearance of any visible tumor, but in some cases a tumor appeared but regressed after a short time. These latter cases also developed an immunity. Only one of the fifty-eight control rats showed spontaneous regression of the tumor. Similar work had been done previously, but in most cases hybrid animals and transplantable tumors of unknown genetic origin were used and the great variation of results might have been due to these factors which were avoided by Goldfeder. This work is particularly important for, as the author states, it gives evidence for the first time that it is possible to render animals of a pure line immune against an autogenous tumor.

Although roentgen radiation has been used for many years in the treatment of tumors and there have been many at-



tempts at the study of its effect on tumors, these have been largely from the standpoint of morphology rather than tissue chemistry. Stowell,<sup>25</sup> realizing that many tumor cells are more sensitive to radiation than the corresponding normal cell types, has done quantitative studies on the thymonucleic acid content of transplantable mammary carcinomas after roentgen radiation. He found that the majority of radiated tumors in rats showed a significant decrease in the amount of thymonucleic acid per unit volume of tissue and a significant decrease in the amount per cell. He states, "The results of these experiments would support a hypothesis that roentgen radiation may alter the molecular structure of vital substances within the nucleus and produce a disturbance of the nucleoproteins, which in some instances is followed by death of the cell. Mitchell has found that ribonucleic acids are increased in the cytoplasm following radiation. The present observations which show decrease in desoxyribonucleic acid in radiated cells suggest that one of the most important intracellular effects of roentgen radiation is the production of an upset in the normal balance and metabolism of both types of nucleic acids." This study is interesting, particularly because it is considered by many that the basis of malignancy may be in these nucleic acids the equilibrium of which Stowell has found to be upset by radiation.

Of the many studies on normal and neoplastic tissue metabolism, the last few years have produced particular concentration on the enzymes in these tissues. Greenstein<sup>26</sup> has done much work in this field and noticed that in all cases where a comparison could be made the esterase activity of mouse tumors was less than that found in the tissue of origin. He also noticed that the esterase

activity of nearly all tumors was low. These facts must be considered as part of the disturbed equilibrium commented upon by Cowdry previously.

An interesting observation by Dunn<sup>27</sup> was made on the behavior of thymus tissue transplanted to a skin wound in rats. A stratified squamous epithelium developed on the surface of skin wounds in old rats when thymus tissue from younger animals of the same strain was put on the wounds. The epithelium seems to be derived from the thymus reticulum cells and the study gives further evidence of the potentialities of these peculiar thymic cells. One could readily speculate on the possibilities of using thymus tissue in wounds but it must always be remembered that these experiments are done using rats of the same strain and for this reason the application of these potentialities to human use is not feasible, but the collection of facts concerning tissue metaplasia is always of value in the study of neoplasia. Biskind and Biskind<sup>28</sup> have been able to produce a tumor of the rat testis by heterotransplantation of infantile testis to the spleen of an adult castrate. The same authors have previously recorded the development of granulosa cell tumors of the rat ovary after transplantation of one ovary to the spleen and the removal of the other.<sup>29</sup> By these methods of transplantation, the authors claim that the estrogen or androgen secreted by the transplanted tissue is secreted into the portal circulation and thereafter inactivated in the liver. It is by this means that the endocrine product secreted is prevented from exerting its normal cyclic inhibiting effect on the pituitary. The excessive secretion of pituitary gonadotropin is thus enabled to act continuously on the transplanted tissue. The tumor developing in the testis within the spleen bore a striking

resemblance to the granulosa cell tumor of the ovary and parts of the testicular tumor suggested the structure seen in an arrhenoblastoma. The further elaboration and continuation of these studies should be very interesting because of the peculiar potentialities of both the ovary and testis in relationship to the pituitary secretions. Since some of the gonadotropic hormones of the pituitary might be given to these animals in addition to those naturally occurring substances, one wonders whether the tumors observed might be more quickly produced or even show variations similar to those observed in the human organism.

Rous and Smith<sup>30, 31</sup> have conducted an excellent and thought provoking series of experiments to determine whether potentialities of epidermal cells for neoplastic changes were inherent within the cells or acquired from some outside source. They implanted skin of mouse embryos into thigh muscles of adults of the same strain and simultaneously introduced methylcholanthrene with the result that epidermal tumors, both benign and malignant, rapidly arose from the implants. They found that growths arose as rapidly from the epidermis of some adults as from similar tissue of the most responsive embryo implants. There seemed to be no reason for the idea that the embryo skin had any special liability to neoplastic change and even the youngest embryos used revealed no definite or additional resistance to neoplastic change. After these discoveries, the authors wondered why neoplasms are so rare at birth, a fact frequently noted in humans as well as in lower animals. The studies suggested a possible reason, for it was observed that although mouse epidermis is as sensitive or more sensitive than other tissues to methylcholanthrene, still the embryo implants exposed to the carcinogen required longer periods to give rise

to tumors than could be offered by the total period of gestation. It was, therefore, supposed that either in mice or humans the birth would occur before any tumor could develop even if a carcinogenic stimulus were acting in prenatal life. The authors state in conclusion, "The findings as a whole render it impossible to suppose that the neoplastic potentialities possessed by transplanted embryo tissues are due to the lodgment in them of tumor-producing viruses as specialized in their effects as those now known, or of precursor agents conferring neoplastic liabilities specialized to the same degree."

**Chemotherapy** - The fascinating field of chemotherapy in oncology is constantly being broadened and at present, as in the past years, the chief weight of study has been on the effect of certain bacterial toxins and extractable substances. Brues and Shear<sup>32</sup> have reported additional work on the use of a *polysaccharide* from culture filtrates of *bacillus prodigiosus*. Four patients with advanced malignant tumors were given injections of this substance, which produces hemorrhage in, and partial or complete destruction of, sarcomas in mice. All the patients died with the tumors, but two showed some relief of symptoms and two showed hemorrhage in the tumors at postmortem examination. This report is one of the early attempts at use of this substance in the treatment of human tumors and future reports now in preparation concerning later work and studies will be even more encouraging. At this stage of investigation there is no suggestion by any of the workers in the field that this or similar substances will cure human tumors, but there is every indication that many tumors are damaged in much the same fashion as they are in animals and this fact alone is worthy of great support for the investigators. Zahl, Starr,

and Hutner<sup>33</sup> tested thirty-eight strains of plant pathogens for tumor-hemorrhage induction by killed suspensions of these organisms and found, as had been previously proposed, that gram-negative bacteria as a class possess a factor, the distinguishing characteristic of which is the ability to produce hemorrhage in implanted mouse tumors. Gram-positive bacteria as a class seem to lack this factor. The exact site of activity of these bacterial products is not known and it seems that necrosis is as important a result of their use as is hemorrhage. Much of the as yet unpublished study of these products will, no doubt, greatly enhance our knowledge and offer much hope for the future.

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## DERMATOLOGY AND SYPHILOLOGY

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## DERMATOLOGY

## The Use and Abuse of Sulfonamides

The introduction of the sulfonamides and, more recently, of penicillin in the therapy of dermatoses has resulted in a considerable controversial literature as to the merits and the ill effects of these therapeutic agents.

The sulfonamides were at first hailed as a group of drugs that offered quick cures in a number of infected dermatoses, but the indications are now better established and most physicians realize the limitations of this group of drugs. In a guest editorial in "Digest of Treatment," Tobias<sup>1</sup> points out that abuses are widespread with resulting sensitiza-

tion and toxic effects, and he abstracts some interesting literature dealing with this problem as well as giving some personal observations.

Dowrie and Abramson have demonstrated that in the field of pediatrics there was no difference in clinical response between sulfadiazine and sulfathiazole. However, the latter produced 7.6 per cent drug rashes while none were produced in their series of sulfadiazine-treated cases. On the other hand, Frish reports that in his series of 65 sulfonamide-induced skin eruptions among military patients, 55 per cent were the result of sulfathiazole medication.

The adverse reactions to the sulfonamide drugs include disturbances of the alimentary tract, skin sensitizations resembling serum disease, toxic effects on the blood cells, bone marrow, and blood pigment, nervous phenomena, and renal changes.

The causes of these reactions include interference with the normal intestinal flora, disturbance of the protective enzymes which help to regulate the defensive mechanism of the body, interference with the synthesis of vitamins, necrosis of the blood vessel walls, acetylation of the urine with precipitation, and free toxic radicles in the blood stream. Longcope has shown that most of the cases resemble serum disease and are caused by conjugated plasma protein-sulfonamide compounds in the blood.

The indiscriminate administration of these drugs for dermatoses, for which there is no experimental or clinical evidence that such therapy will prove of value, jeopardizes the patient and the reputation of the drug.

**Oral medication** with the *sulfonamides* is indicated in erysipelas, widespread impetigo, impetiginous eczema, hidradenitis suppurativa, chancroid, the early stages of lymphogranuloma vene-

reum, vaccinia, actinomycosis, cellulitis, lymphangitis, some types of pyoderma gangrenosum, carbuncle, dermatitis herpetiformis, and the septic complications of pemphigus, and other widespread skin infections. When employed in the above conditions, the sulfonamides should not be used for longer than ten days. If they are going to be effective, the eruption will respond within that time or not at all.

**Local applications of sulfonamide** preparations are not frequently indicated. At least other drugs, less toxic and with a lower sensitizing index, should be tried first. It should be remembered that the sulfonamides are bacteriostatic and bactericidal. They should not be used in the treatment of dermatoses which are not of bacterial origin, such as psoriasis, ringworm, and contact dermatitis.

Indications for local use include impetigo, infected traumatic dermatitis, ecthyma, impetiginized eczema, streptococcal dermatitis, and pyogenic paronychia. However, in all the foregoing diseases, the sulfonamides should be used only as a last resort when other forms of therapy have failed or when withholding the drug might result in scarring or deformity.

An important contraindication is a history of previous sensitization. Eczematoid dermatitis, or so called weeping eczema, should never be treated with sulfonamide applications because the exposure of the rete permits greater absorption and a break in the natural defense mechanism of the skin.

The prophylactic use of the sulfonamides in certain conditions merits some discussion. The use of *sulfathiazole ointment* on the skin of new born infants as a preventive of impetigo has been successful during epidemics, but its routine use is to be deprecated.

Danger of sensitization exists from the routine use of sulfonamide ointments or powders on cuts, bruises, and vaccination sites. The same holds true for venereal prophylaxis, in which case the patient may still become infected with sulfonamide-resistant gonococci or Ducrey's bacilli. The value of *sulfonamide chemoprophylaxis* as advocated by Coburn in meningitis, common colds, pneumococcal infections, rheumatic fever, and by others in simple burns and as a preoperative measure is also questionable.

The abuse of sulfonamide medication may be summed up as follows:

1. If the patient has toxic symptoms from the first course of the drug, the second course may soon give rise to serious reactions.

2. Prolonged use of sulfonamides with no beneficial effect after ten days may result in toxic reactions.

3. The empirical use of sulfonamides is not without danger, and precious time may be wasted.

4. Complications of sulfonamide therapy, such as cyanosis and erythema, may be confused with an extension of the disease under treatment. In many cases, the dosage may be increased or local sulfonamides prescribed with serious consequences.

5. Inadequate dosage often elicits an unsuccessful response. Either the drug should be administered properly or not at all.

6. The use of local sulfonamide preparations for various dermatoses that baffle the practitioner is not only a waste of money and time, but may result in incapacitating sensitization.

7. It is a mistake to continue with the sulfonamides and defer surgery, once suppuration is apparent. Nothing is gained but subclinical suppression.

The detection of sulfonamide sensitization by intradermal skin testing as advocated by Leftwich is not practical or trustworthy at the present time. Negative tests may occur in patients who may later show toxic effects from the drug. The test is made by using serum obtained from a patient receiving sulfonamide medication.

Desensitization in known sensitized patients with small doses (0.13 Gm.) of a sulfonamide every hour for 12 hours has not proven successful in all cases, but is worthy of trial when need of the drug is imperative.

Treatment of sulfonamide reactions consists of *stopping the drug* and employing *detoxifying measures* including the *soluble liver extracts* containing *folic acid* as advocated by Longcope.

The value of large doses of ascorbic acid in the treatment and prophylaxis of sulfonamide reactions has been questioned by Dowrie and Abramson and others.

### Penicillin in Cutaneous Disease

At a large military hospital, Taylor and Hughes<sup>2</sup> used penicillin in the treatment of sycosis barbae, impetigo contagiosa, furunculosis, and other varieties of the large group of eruptions known as the infective dermatoses. Penicillin was applied locally in various ways in an endeavor to find the most efficient and most economical mode of application. The preparations that were tried included crude penicillin filtrate in a base of equal parts of lanette wax, liquid petrolatum, and water; calcium penicillin in a base of 30 per cent lanette wax in water; sodium penicillin in a base of 30 per cent of lanette wax; sodium penicillin in aqueous solution; penicillium mold of about fourteen days' growth, and penicillium mold crushed up in a base of 30 per cent lanette wax in water. Before

treatment, the lesions were examined bacteriologically. Cultures on blood agar were made with a wool swab. The plates were incubated for twenty-four hours or longer, the organisms growing were identified, and a rough colony count was made. All organisms grown were tested for sensitivity to penicillin and all staphylococci had their coagulase production assessed. During treatment, daily cultures were made in a similar way. The authors found that penicillin is effective in the local treatment of certain skin diseases caused by cocci. The most satisfactory method of treatment of sycosis barbae and impetigo is to *spray* the *lesions* with an *aqueous solution* containing 200 units of *penicillin* in each cubic centimeter. An adequate dose of penicillin from the start is essential to prevent the development of penicillin-fast organisms. A strength of 200 units of *penicillin* in each cubic centimeter or 400 units per gram of lanette base seems to be sufficient. The pain in deep-seated lesions (furuncles) is much relieved after application of penicillin. An underlying seborrheic state in cases of sycosis and impetigo is liable to cause relapse soon after cessation of treatment and necessitate further courses of treatment. The appearance of penicillin-insensitive organisms indicates that further treatment with penicillin is of little value.

According to Kierland,<sup>3</sup> penicillin applied locally is of value in primary and secondary infections of the skin and in clinically noninfected eczematous dermatitis, and has been reported the treatment of choice for so-called tropical ulcers in a study made in the South Pacific Theater.

*Penicillin* was used in the form of an *ointment*, 200 units per Gm. of *lanolin* or *emulsion base*, *medium* (U. S. Army), or a wet dressing, 200

units per cc. of *distilled water* or normal *saline*. The base or vehicle used apparently did not affect the clinical results. Approximately 10 per cent of patients complained of increased burning and pruritus of the skin.

Results of treatment are analyzed as follows:

**Eczematous Dermatitis** Wet dressings in the early phases and ointment after exudation had subsided. Of sixteen patients clinically noninfected, two improved markedly, seven moderately, five were unimproved, and two became worse. Of twenty three patients with concomitant pyogenic infection, five improved markedly, fifteen moderately, two were unimproved, and one became worse.

**Ecthyma** (ten patients) "Penicillin ointment produced better results than any other therapeutic agent" in six patients with so called tropical ulcers, all healing in three weeks. In the other four cases, "excellent" results were obtained in two and "moderate" in two.

**Impetigo** Of nine cases of bullous impetigo, seven improved and two were unimproved. Of seven cases of crusted impetigo, six improved and one was unimproved.

**Infected Trichophytosis** (six cases)

Excellent results in four and moderate in two.

**Infected Dermatitis Venenata** (three cases) Excellent results in two and one became worse.

**Exudative Crural Intertrigo** (three cases) Two improved, one stationary.

"Excellent" results were obtained in two infected thermal burns and in one case of dermatitis repens. In one case of sycosis vulgaris, temporary improvement occurred but pustules recurred when treatment was discontinued.

Bacteriologic cultures made in 40 per cent of the patients routinely revealed

either hemolytic streptococci or hemolytic staphylococci. Cultures remained positive in most instances for three to fifteen days after clinical evidence of infection had disappeared.

### Skin Lesions Attending the Use of Penicillin

This important phase of penicillin therapy has been reviewed by Flinn, McGee, Featherston, and Kern.<sup>4</sup>

Urticaria is not an uncommon occurrence during the administration of penicillin. Lyons found urticaria in 12 of 209 patients receiving penicillin. Keefer and his associates described 14 instances of urticarial eruptions in their review of the use of penicillin in 500 patients. Dawson and Hobby noted 3 instances of urticaria among 100 patients receiving the drug, and Stokes found urticaria in 2 of 182 patients so treated.

A summary of experiences with penicillin-treated patients reported in medical literature during the past two years indicates that the incidence of urticaria during the use of the drug is approximately 3 per cent.

Such urticaria is usually characterized as being a mild and transient affair. Most authors have found that such reactions are not accompanied by other and more serious manifestations of allergy. In numerous instances, the urticaria has subsided spontaneously either with or without temporary discontinuance of the penicillin. Keefer observed in 1943, "Whether these reactions are due to some impurity in the penicillin cannot be stated at present. In several cases in which penicillin has been given after an attack of urticaria, there have been no signs of recurrence."

Criep performed intradermal tests with penicillin on a twenty-three-year-old male who developed massive gen-

eralized urticaria following the administration of the drug. Intradermal tests were positive to penicillin, whereas penicillin (extract of spores) gave negative reactions.

Feinberg selected ten patients who gave positive skin reactions with various extracts of penicillin including penicillium notatum. Intradermal tests of penicillin gave uniformly negative reactions, suggesting that it is not the spores of the fungus which accounts for skin reactions of penicillin-treated patients.

### Other Skin Reactions

Reports of other and more significant manifestations of skin allergy, such as dermatitis venenata, are appearing concomitant with the increased clinical use of penicillin. Pyle and Rattner found an instance of contact dermatitis in an Army medical officer.

Graves, Carpenter, and Unangst reported the occurrence of an acute vesicular dermatitis in a white forty-six-year-old male, three hours after the first injection of penicillin.

Binkley and Brockmole reported instances of two physicians (hospital interns) who developed contact dermatitis on the face, hands, and arms. The lesions healed when these physicians avoided exposure to solutions of penicillin.

Silvers found skin sensitivity in a chemist, age thirty-six years. The rash affected the eyelids and penis. In this patient the patch test with yellow amorphous sodium penicillin was positive. A patch test with the solution of pure white crystalline sodium penicillin was negative. The author concluded that the impurities present in the yellow amorphous sodium penicillin were responsible for the contact dermatitis.

A bullous dermatitis from parenteral injection of penicillin has been seen and reported by Morris and Downing.

A case is reported by the authors in which severe urticaria developed from one brand of penicillin. Intradermal testing showed a positive reaction for this brand and for two others. A fourth brand showed no reaction by intradermal test and was administered to the patient without allergic manifestation. On one occasion, the offending brand was given again with repetition of the urticaria, confirming the original observation of sensitivity to this brand. Some time later the patient had lost this sensitivity as determined by intradermal test and was then given this particular brand without allergic reaction.

The authors suggest that if urticaria occurs in the administration of penicillin, skin testing with other brands may reveal a product to which the patient is not sensitive. Continuation of treatment may then be carried out without what might otherwise be a serious interruption.

### Contact Dermatitis

According to Gross,<sup>5</sup> the dermatologist must be an excellent detective to solve the many mysteries that the non-specific eczema group presents.

Generally speaking, the term eczema is an ambiguous one, and is employed rather loosely. Indeed, it is the veritable scrap heap of dermatology.

It is my impression that the etiologic agents of the idiopathic eczema group can be elicited by certain clues which would enable the physician to place it in the contact dermatitis group, thereby narrowing this broad field and facilitating the diagnosis.

The following criteria are of prime importance in searching for the noxious agents:

1. Sudden onset of the eruption following exposure to the offending agent.

2. Marked improvement of the dermatitis when the offending agent is removed.

3. Recurrence or exacerbation of the eruption when exposed to the offending agent again.

4. Positive patch tests.

Of the four aforementioned criteria, the last is the least important.

A positive patch test is significant (except when a primary irritant has been employed); however, a negative patch test does not necessarily rule out the rôle that the offending agent played in the production of the dermatitis.

In order to interpret the criteria properly, a sound significant history should be recorded and the powers of observation should be enhanced.

Contact dermatitis does not necessarily have to be an acute affair. In many instances, it is a low grade or subacute eruption.

Generally speaking, if an eruption does not lend itself readily to well known dermatologic entities, such as seborrheic dermatitis, pityriasis rosea, psoriasis, etc., it would be well for the physician to rule out the possibility of a contact dermatitis.

To properly treat the patient, it is best to evaluate the findings as presented before treatment is instituted. Unfortunately, many dermatologic patients are treated empirically with pet prescriptions and the latest proprietaries, resulting in a superimposed contact dermatitis which not only masks the original condition, but usually produces widespread "id" eruptions.

It is wiser and easier to recognize the offending agent, avoid its contact, and employ soothing, bland, local applications rather than to subject the patient eventually to extensive costly treatments.



To enable the physician to search for and elicit clues as to the contact origin of dermatitis, I have listed the following tables comprising the likely irritants and areas of their involvement:

### CONTACT DERMATITIS

#### Irritants and Areas of Involvement

TABLE I.

##### *Man.*

##### *Scalp and Forehead.*

Phylacterics.

##### *Eyebrows and Eyelids.*

Hair tonics.

Substances used by wife.

##### *Ears.*

Shaving creams and lotions.

##### *Circumoral Region.*

Pipes, chewing tobacco.

Cigars.

##### *Neck and Face.*

Shaving preparations.

Starch in collar.

Collar button.

Hair preparations.

##### *Breasts.*

Suspenders.

##### *Axillae.*

Shaving lotions.

##### *Trunk.*

Matches, match box.

Lighter fluid and lighters.

##### *Arms and Forearms.*

Shaving lotions.

##### *Hands.*

Overcoat.

##### *Groin and Genitals.*

Shorts, truss.

Bathing trunks, articles in pocket, contraceptives.

Suspensory.

##### *Legs.*

Dry cleaning fluids.

Trousers.

Garter.

Garter clasp.

Sulfur (match box dermatitis).

Articles in pockets.

##### *Feet.*

Oil from trousers of workers.

Dye in socks.

TABLE II.

##### *Woman.*

##### *Scalp and Forehead.*

Hair dyes, wave sets, perfumes, hair pins, hair net, combs, head dress.

##### *Eyebrows and Eyelids.*

Eyebrow pencils, mascara, lash lure, nail polish.

Substances used by husband.

##### *Ears.*

Earrings.

##### *Circumoral Region.*

Lipstick.

##### *Neck and Face.*

Nail polish, jewelry, hair preparations, perfumes, wave sets, facial cosmetics, furs.

##### *Breast.*

Straps, zippers, brassiere, rubber, perfume.

##### *Axillae.*

Shields.

##### *Trunk.*

Zipper, girdle, and panties.

##### *Arms and Forearms.*

Jewelry, cosmetics, perfumes, depilatory.

##### *Hands.*

Jewelry, fur coats, nail polish, nail polish remover.

##### *Groin and Genitals.*

Contraceptives, sanitary napkins, sanitary belt, medication (douche).

##### *Legs.*

Garters, garter clasp, depilatory, hose, theater seat, galoshes—fur lining.

##### *Feet.*

Nylon, dyed shoes.

TABLE III.

##### *Both Sexes.*

##### *Scalp and Forehead.*

*Cosmetics*—hair tonics, hair dyes, wave sets, shampoos, perfumes.

*Medication*—ointments and lotions.

*Head wear*—hats, cleaning fluids, dyes, hat bands.

##### *Eyebrows and Eyelids.*

*Cosmetics*—hair tonics, creams used on face.

*Medication*—nasal sprays and secondary to scalp applications.

##### *Ears.*

Earphones, spectacles, earpieces, scalp and hair preparation.

*Circumoral Region.**Cosmetics.*

*Toilet Articles*—tooth paste, tooth powder, mouthwash, tooth brush.

*Foods*—fruits, raw vegetables, and chewing gum.

*Metals*—wind instruments, dentures, cigarettes.

*Neck and Face.**Cosmetics.*

*Wearing Apparel*—dyes in cloth, scarves, wool neck pieces, cleaning fluids, sprays (moth-fly).

*Miscellaneous*—blankets, plants, dust, fumes.

*Breast.*

Rubber, cosmetics, rayon, dyes in pajamas and articles of clothing.

*Axillae.*

Deodorants, dyes in clothing, cleaning fluids, depilatory.

*Trunk.*

Soap, articles of clothing, local medication.

*Arms and Forearms.*

*Clothing*—rayon, wool.

*Metals*—bracelets, wrist watches.

*Miscellaneous*—leather, lacquer in jewelry, table wood varnish, oil cloth.

*Hands.*

*Chemicals*—alkalies, solvents, all chemicals used in professions, trades and avocations, soap, soap powders.

*Cosmetics and Wearing Apparel*—gloves, jewelry.

*Oils and Waxes*—vegetable oils (plants and fruits), polishing wax.

*Miscellaneous*—newspaper, cigarettes, paints, dyes, lacquer, antiseptics, soaps, local medications, anything may become an irritant.

*Groin and Genitals.*

Dyes in clothing, medication, toilet seat rubber-pads.

*Legs.*

Clothing, carpet, house dust.

*Feet.*

Dyes in socks, leather, shoes, rayon, nylon, medication.

**Overtreatment Dermatitis**

Gaul<sup>6</sup> points out that almost every day skin lesions are observed that have been made worse by imprudent topical

therapy. Even neoplasms are not spared from the "put something on it" impulse. Apparently all that the skin has to do is to complain a little—an evanescent erythema or pruritus—and it is impulsively daubed with the nearest thing at hand. This practice often causes needless complications, loss of gainful work, unnecessary expense and hospitalization, even the acquiring of cutaneous sensitization.

Gaul reports a series of cases which illustrate the cause of overtreating dermatitis. The initial skin lesion registered complaint—increased erythema, edema, and weeping—from the first application. Instead of the preparation being removed, something else was applied and the more the lesion complained, the greater was the variety of applications applied. The admixture of antipruritics, antiseptics, astringents, rubefacients, keratolytics, fungicides, oxidizing agents and reducing agents in various vehicles unleashed on innocent lesions a veritable chemical maelstrom. The lesions do weep, in fact, huge tears of chemical irritation.

It should be emphasized that the saline compress and the colloidal clay were not instrumental in healing the dermatitis. The former served to free the skin of irritants, the latter, a covering while the skin healed. The continuation of either, beyond their period of usefulness, would have complicated and delayed the involution process.

The creation of the Council on Pharmacy and Chemistry served to rob of glamor the old oral concoctions and potions; it sifted the wheat from the chaff. Today oral drugs are fairly well defined. Dosage, indications, and contraindications are familiar to all. There is constant vigilance for signs and symptoms of toxicity. Topical drug therapy, on the other hand, is generally speaking

still in the stage of "try—stop—try." In the treatment of skin disease, the admonition, "Try this preparation; if no improvement, try this one," and so on, is familiar. It is this practice that causes overtreatment dermatitis. In skilled hands this "try—stop—try" method is controlled. In unskilled hands, which treat the major portion of acute dermatoses, too much treatment often results. It is the acute dermatoses that require the greatest treatment, control, and consideration. It seems that a concise chemical and pharmacologic evaluation of drugs used on the skin might lead to a decline of the incidence of overtreatment dermatitis. That is another sifting of the wheat from the chaff and this time to rob of glamor the cutaneous drugs, irrespective of the real or fancied virtues of the particular vehicle.

### The Pathogenesis of Atopic Eczema

According to Simon,<sup>7</sup> recent experiments on the rôle played by human dander in the etiology of atopic eczema have yielded information which have bearing on the pathogenesis of this disease.

Patch tests with human dander were positive on twenty-six of thirty-one children with atopic eczema. The reactions to tests were areas of eczema at the sites of application. Typical areas of eczema were produced by rubbing human dander on uninvolved skin areas. Intradermal injection of dander extract failed to reproduce the lesions although, in a large proportion of adults with this disease, urticarial reactions were produced by intradermal injections and by scratch test, and reagins for human dander were demonstrated. An important allergenic excitant of this disease, therefore, is capable of penetrating into the epidermis from without, either directly or by way of hair follicles or sweat glands and of

reproducing the lesions, while this same substance injected intradermally fails to reproduce the lesions.

Simon believes that the most important allergenic excitant of atopic eczema thus far described is human dander. The allergen reaches the sensitive tissue by penetration into the epidermis from without. The predilection of the disease for certain skin areas cannot be explained on the basis of a comparative increased specific allergic sensitivity of these areas, but may partially be explained on the basis of proximity to the scalp and on factors favoring accumulation, solution, and penetration of dander allergen. Injury of the cornified layer favors penetration of the allergen. Scratching is harmful not only because it injures the skin but also because the finger nails are contaminated with dander. The allergen of human dander was found to be soluble in physiological solution of sodium chloride but not in ether or alcohol. The epidermis probably plays an important rôle in this disease. There are reasons for believing that the urticarial reactions to foods, inhalants, and even human dander frequently associated with this disease are coincidental and irrelevant from an etiologic standpoint; that the disease is, at least in part, an epidermal manifestation of atopy. The existence of other important causative factors, in addition to surface contact with human dander, is indicated.

### The Treatment of Herpes Zoster by Paravertebral Procaine Block

A recent discussion of herpes zoster plainly indicates the unreliability of current therapeutic methods, but fails to mention the one form of treatment which is likely to provide instantaneous and complete relief from pain. This method, which consists in *blocking* appropriate

*sympathetic ganglions* with *procaine hydrochloride*, is not as well known as it should be because to our knowledge it has been described only once in the American literature—the article by Street. However, Rosenak, of Budapest, had previously reported a larger series of cases. Findley and Patzer<sup>8</sup> record their experiences with this treatment in four cases because they are persuaded that all other methods are obsolete. The

The patient is placed in a supine position with the head in the midline and slightly extended. A point is selected two fingerbreadths above the sternoclavicular junction and just medial to the pulsations of the common carotid artery. A 22 gage spinal puncture needle is then inserted straight down, the operator aiming to hit the transverse process of the seventh cervical vertebra. The needle is then withdrawn about 0.25 cm. If no blood is aspirated, 10 cc. of 1 per cent procaine is injected slowly; the needle is left in place until Horner's syndrome appears; this usually occurs within two

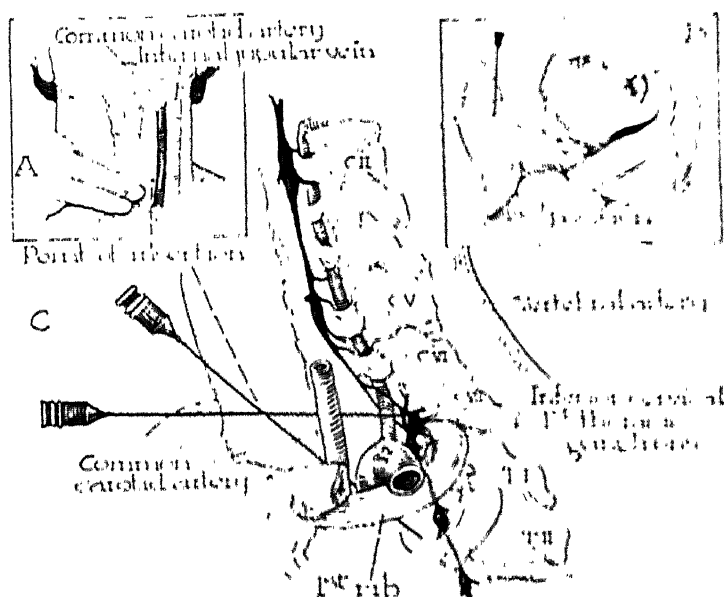


Fig. 1.—Technic of injecting the lower cervical and upper thoracic sympathetic ganglions (Findley, T. and Patzer, R.: J. A. M. A. 128:1217 (Aug. 25) 1945.)

total number of cases reported, including theirs, is twenty-nine and in only two of these was there failure to experience prompt and lasting relief from pain.

### Technic

**Technic**—The technic of sympathetic block is not difficult and is practically without danger if only procaine or allied anesthetic drugs are used and if one is familiar with the anatomy. To block the cervicodorsal and the second and third thoracic sympathetic ganglions, we prefer the anterior approach. By this method 10 cc. of 1 per cent *procaine hydrochloride* is used to flood the region of the cervicodorsal ganglions and another 10 cc. to flood the region of the second and third thoracic sympathetic ganglions.

or three minutes. The needle is then withdrawn about 1 cm. and directed into the thorax, care being taken to keep it close to the body of the vertebrae near the junction of the transverse process. The region of the second and third sympathetic thoracic ganglions is then infiltrated with 1 per cent procaine hydrochloride.

### Pruritus in General Medicine

Simple pruritus occurring as part of a symptom complex or as a single condition may be the first warning of serious disease. Appraisal of the symptom is complicated by absence of objective findings and by the fact that itching

is of pathologic significance only in proportion to the intensity. Disturbances capable of influencing both physical and psychic states have been tabulated by Kingery.<sup>9</sup>

1. *Toxemias*: Resulting from (a) isolated foci, such as the teeth, etc.; (b) absorption from a malfunctioning or infected gastrointestinal mechanism, and (c) those originating in a skin absorbing bacterial or fungus products.

2. *Products of Abnormal Metabolism*: Impaired carbohydrate metabolism with

tation; external medicaments, including sulfur, various antiscabietics, the mercurials, nupercaine and benzocaine; household soaps, clothing, and materials containing dyes; cosmetics, including perfumes, nail polish, hair lacquer and mascara; various industrial irritants.

5. *Endogenous Causes*: Morphine and its derivatives; sedatives, including the barbiturates; drugs containing phenolphthalein; the arsphenamines, sera and vaccines; foods, including wheat, eggs, milk, fish, and seafoods; inhaled

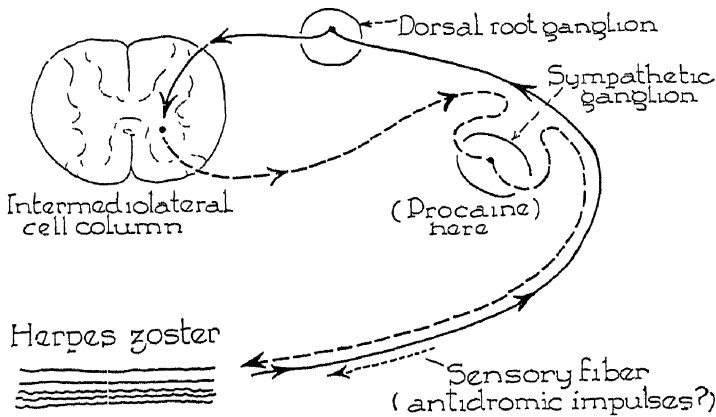


Fig. 2—Schematic representation of the vicious cycle responsible for segmental vasospasm in herpes zoster. (Findley, T. and Patzer, R.: J. A. M. A. 128: 1218 (Aug. 25) 1945.)

or without true diabetes, impaired liver function with clinical or subclinical jaundice, abnormal renal function with resultant changes in the chemistry of the blood stream with or without hypertension, obscure abdominal carcinomatosis, and endocrine disturbances—thyroid, ovarian, menopausal episodes, etc.

3. *Abnormalities of the Blood and Blood-forming Organs*: Anemias of various types, and blood dyscrasias—the lymphogranulomatous diseases, including mycosis fungoides—Hodgkin's, and the leukemias. Cutaneous symptoms may long precede positive laboratory evidence of the disease.

4. *External Chemical Causes*: Plants, flowers, and various other forms of vege-

substances, such as pollens, dusts, and spores.

6. *Neurogenic and Psychogenic Causes*: Inflammatory and destructive processes, including zoster, tabes, and tumors; functional neuroses, including "tension states," hysteria, and emotional disturbances of various types.

As causal therapy may entail long periods of study and employment of a variety of clinical and laboratory procedures, symptomatic treatment constitutes the first therapeutic measure. One or several of the following procedures may be employed.

1. *Sedatives: Bromides*, 0.32 to 0.65 gm., three or four times daily by mouth, or 5 cc., 10 cc., etc., of a 10 per cent

solution intravenously (daily injections) ; *Tinct. Cannabis Indica*, 0.61 cc. three times a day gradually increased to 1.54 cc. three times a day; morphine occasionally — recognizing its potentialities.

2. *Dietary Regulation*: Depending on the type of case—in general, *avoid red meats, sea foods, and carbohydrates, force fluids* and secure *free elimination*.

3. *Foreign Protein Therapy*: Given in intramuscular injections of (a) a 4 per cent suspension of *milk protein*, 1 to 5 cc. every three to seven days; (b) intravenous *typhoid vaccine*. Patients should be warned of febrile reaction.

4. *Autohemotherapy*: Simple and safe. Ten to 20 cc. from arm to buttocks every one to three to five days.

5. *Generalized Ultraviolet*: Frequent suberythema doses are preferable to infrequent large doses.

6. *X-ray*: Perhaps best, but must be given in carefully and accurately recorded amounts.

7. *Topical Remedies*: Baths (bran, oatmeal, linit, alkaline—soda), at least thirty minutes at least twice daily, never rub the body dry, and should be at comfortable, not high, temperature; wet compresses, some soft material, not gauze; lotion, usually oil, is added to combat drying effect; salves and pastes, for the most part on subacute and chronic, never on moist, oozing surfaces. In each may be included phenol, 1 to 2 per cent; methol,  $\frac{1}{6}$  to  $\frac{1}{4}$  per cent, or camphor, 1 to 3 per cent.

### Some Phases of Vitamin Therapy in Dermatology

Vitamin therapy in the dermatologic field is used for a variety of diseases, which may be divided into two groups: (1) The true and established vitamin deficiencies, and (2) dermatoses in

which a true vitamin deficiency is either debatable or undemonstrable but for which vitamin therapy appears to be of benefit. Some dermatoses of the latter group are the subject of discussion by Obermayer and Frost.<sup>10</sup>

Vitamin therapy in dermatology presents certain peculiarities which must be appreciated if satisfactory results are to be achieved. For most diseases which yield to treatment with vitamins, infinitely higher doses are required than are provided by dietary measures or by the administration of commercially advertised vitamin concentrate mixtures. Moreover, the route of administration plays at times an important, if yet unexplained, rôle. In selecting vitamin products, one has the choice of synthetic vitamins and the natural concentrates. The pure crystallized chemical compounds would be preferable because the vehicle for the natural concentrates may be the source of allergic reactions. However, there are indications that, as in the case of estrogenic substances, the effect of the two types may not be identical (Stokes).

An important and as yet not generally recognized effect of a high intake of vitamins A, C, D, and the B complex is its aid in the control of the allergic state. In certain chronic recurrent inflammatory dermatoses, for instance, the dry form of neurodermatitis (atopic dermatitis) and some forms of chronic urticaria, it is well established that the accompanying phenomena of dermal hypersensitivity, indicated by positive reactions to dermal tests, vary in intensity from time to time in the same patient. Any therapy which aids in the control of that allergic link is a welcome addition to the management of these dermatoses. How this effect is accomplished by vitamin therapy is not clear. Stokes has expressed the opinion that it may

be due in part to the action of the vitamin B complex on the intestinal tract and perhaps to the antidermatitis and hypochlorhydria preventing fractions. We can confirm the beneficial effect of large doses of *vitamin B complex* in the therapy of this group of dermatoses. It may be administered in the form of injections of *crude liver extract* two or three times a week, or it may be given by mouth.

Large doses of vitamin A seem to affect a large number of dermatologic diseases by their influence on the integrity and resistance of epidermal and epithelial surfaces. It has been claimed that vitamin A serves as an important buffer against pyogenic infection, but it seems probable that its effect is only indirect and that excessive keratinization of epithelium paves the way for infection. The mechanism of the effect of vitamin A on the epithelial tissues has not been explained.

The value of vitamin A therapy in the treatment of patients with an abnormal tendency to formation of caluses is definite. Successful treatment of corns with this vitamin was reported by Straumfjord. Keratosis blennorrhagica likewise yields to the administration of vitamin A.

Although the influence of vitamin A therapy on keratotic changes in the follicles is somewhat better understood than its effect on diffuse keratotic changes, because follicular keratinization is one of the outstanding symptoms produced by true vitamin A deficiency, the situation is by no means clear. While it is reported that ichthyosis, for example, is not benefited by vitamin A therapy, asteatosis, lichen pilaris, and lichen spinulosus seem to respond to administration of the vitamin. The beneficial effect of vitamin A therapy on the two rare and obscure follicular dermatoses,

keratosis follicularis and pityriasis rubra pilaris, has been definitely established.

The recent report by Straumfjord has awakened interest in the relations of vitamin A therapy to acne vulgaris. Straumfjord has made the claim that the daily administration of 100,000 U.S.P. units of *vitamin A* for periods of from nine to eighteen months resulted in the disappearance of the lesions of acne in all but 3 of 100 cases. Such startling results in the treatment of a disease which is admittedly of multiple causation can hardly be accepted without confirmation. Vitamin A therapy is undoubtedly of benefit in the handling of some forms of acne vulgaris while others do not seem influenced by it.

Cheilosis was formerly believed to represent uniformly a riboflavin deficiency, but it is emphasized that factors unrelated to vitamins, such as epithelial hypersensitivity and anatomic conditions, may be important in its genesis.

### Three-Hour Treatment of Scabies

A three-hour outpatient treatment of scabies which effected a cure in 217 of 266 patients is reported by Major Simon S. Rubin and Capt. Harvey Blank, M.C., A.U.S.<sup>11</sup> The method consists of a thorough cleansing of the patient's body and application of a modified *Oppenheim ointment*, composed of precipitated *sulfur*, 48.0; *potassium carbonate*, 19.2; *lanolin*, 24.0, and *petrolatum*, q.s. ad., 240.0.

First, the patient scrubs himself thoroughly for fifteen minutes with soap and brush, paying particular attention to favorite sites of scabies, such as the interdigital spaces, the wrists, the elbows, axillary folds, abdomen, penis, thighs, and buttocks. The face and scalp are not treated. The patient then takes a warm bath or shower and scrubs his body again with soap for thirty minutes.

After the patient's body is rinsed and carefully dried, the ointment is applied from neck to toes, special care being taken to cover the sites of the burrows. The patient is next wrapped in a sheet and two wool blankets and put to bed in a warm room. Two hours later the patient takes a shower bath, removes all traces of the ointment with soap and, after drying, covers his body with a thin layer of *zinc oxide paste*.

During treatment all the clothes and blankets of the patient are sterilized by autoclaving; linen is laundered and bedding aired thoroughly. Examination for scabies of all soldiers sleeping in the same hut or barracks is routine.

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## SYPHILOLOGY

In any present day discussion of syphilis, chief interest centers on the subject of penicillin therapy. A review of the medical literature of the past year dealing with penicillin reveals no outstanding paper that gives a complete evaluation of penicillin therapy in syphilis to date, but this is only to be expected of any new therapeutic agent in a disease

such as syphilis. Years of research, clinical studies, and follow up of cases are required for the evaluation of any anti-syphilitic remedy. Some of the articles are worthy of brief mention to bring out single individual facts about penicillin. Thus Osmond<sup>1</sup> reports a case in which the appearance of symptoms of syphilis was delayed by penicillin treatment for gonorrhea and the author suggests a period of observation of at least three months, preferably six months for every patient receiving penicillin for gonorrhea; and Hailey<sup>2</sup> reports a case of syphilitic infection marked by inadequate penicillin therapy for impetigo. In the following paragraphs, other articles on penicillin are quoted at greater length, after a review by Moore<sup>3</sup> on the wider subject of "The Chemotherapy of Syphilis."

### The Chemotherapy of Syphilis

The history of the chemotherapy of syphilis, which covers 451 years, from 1493 to the present, may be divided into three periods: the first from 1493 to 1903, the second from 1903 to 1943, and the third from June, 1943, to the present. Moore summarizes the events of the first, notes the accomplishments and confusions of the second, and outlines in some detail the developments of the third.

Throughout all three periods, the problem of time dose relationship has been constantly present, regardless of what chemotherapeutic agent was being used, but not until the late 1920s was any organized effort made to solve it. Then the League of Nations and the Cooperative Clinical Group undertook a systematic study of the results of the various schedules of treatment. The effects of prolonged *arsenical bismuth* treatment are now fairly well known, as



are the immediate results of the more intensive methods. The late results of the intensive methods will not be available for another generation.

In June, 1943, Mahoney, Arnold, and Harris demonstrated that penicillin was effective in early syphilis in rabbit and in man. Because of the importance of the control of the disease in conserving manpower in wartime, an organized investigation of the uses of the drug was begun with the cooperation of the military and governmental agencies and civilian clinics and laboratories.

Preliminary results of these studies permit certain general statements concerning the treatment of syphilis with *penicillin*:

1. Multiple injections are required for the treatment of early syphilis.

2. The intramuscular route of administration is satisfactory; intrathecal injections are not necessary in neurosyphilis and probably not in late neurosyphilis.

3. The optimum interval between injections is three to six hours.

4. Total doses of 60,000 to 1,200,000 units administered at 3-hour intervals day and night for 7½ days give practically identical immediate results.

5. The relapse rate is in inverse ratio to the total dosage, 60,000 units giving approximately 100 per cent relapse, a dose of 1,200,000 units giving a relapse rate of only 15 to 20 per cent.

6. The rate of relapse in a very large dose (2,400,000 units) seems less frequent, but data are insufficient to furnish proof.

7. Reducing the duration of treatment by half is not helpful.

8. Lengthening the interval between injections to twelve hours is unsatisfactory, but whether there is any material difference between the three- and the six-hour interval is undetermined.

9. Penicillin in combination with an arsenoxide may be more effective than either drug alone.

10. *Penicillin* is apparently effective in early syphilis treatment resistant to *arsenic* and *bismuth*, in the prevention of congenital syphilis in infants born of recently infected mothers, in early neurosyphilis, in infantile congenital syphilis, and in relapsed patients.

11. Four dose schedules are under trial for use in neurosyphilis, the phase of late syphilis most studied so far.

12. A trend toward seroreversal of the blood test following the use of penicillin in late syphilis is evident.

13. Reactions from penicillin are negligible except for the Jarisch-Herxheimer reaction.

A method for use in ambulatory patients is essential, since the present minimum requirement of ten days' hospitalization poses an economic problem.

The history of the treatment of syphilis during the past 450 years indicates the desirability of the continuation of an organized, nation-wide, governmentally sponsored study of the problem.

### Penicillin in Treatment of Early Syphilis

Nelson and Duncan<sup>4</sup> report the immediate results of *penicillin* treatment of six patients with early syphilis resistant to *arsenic* and *bismuth* compounds. Each of the patients had early syphilis and, in all, the cutaneous and genital lesions had shown either progression or failure to heal while under treatment with adequate amounts of trivalent *arsenicals*, usually combined with *bismuth*. The cutaneous lesions in all of the patients were of the psoriasiform type, and spirochetes could be demonstrated in the material from their lesions in five of the six patients. In general, treatment with penicillin was carried

out in a manner similar to that used for patients with early syphilis who had not had previous arsenotherapy. Varying dosage schedules were employed. On the basis of available information, patients with arsenic bismuth resistant syphilis should receive 2,400,000 units of penicillin intramuscularly in sixty injections of 40,000 units each given every three to four hours day and night. Cutaneous or febrile Herxheimer reactions were observed within the first twenty-four hours in two patients. Spirochetes disappeared from all lesions in ten to twenty-six hours after onset of treatment. The cutaneous and genital lesions usually showed prompt healing. Arsenic bismuth resistant syphilis represents a public health hazard, because these patients are infectious. This infectiousness is quickly controlled by penicillin.

### Rapid Treatment of Early Syphilis with Small Doses of Penicillin

Binkley and Kile<sup>5</sup> report the results of the treatment of 159 patients with small doses of penicillin for early syphilis according to an assignment by the Penicillin Panel of the Subcommittee on Venereal Diseases, National Research Council.

Three schedules of treatment were used:

(1) A total dosage of 60,000 units of *penicillin* given intravenously in a solution of *sodium chloride* in injections of 1000 units each at 3-hour intervals for 7½ days; (2) penicillin as in schedule 1 plus a total of 320 mg. *mapharsen* in doses of 40 mg. daily for 8 days; (3) a total of 300,000 units of penicillin in injections of 5000 units each at intervals of 3 hours.

Before participating in the studies of the Panel, the authors had treated 10 patients with 1,200,000 units of penicillin for early dark field positive syphilis.

Seven of this group have been observed for a period of 1 year and are clinically and serologically well.

Of thirty-one patients treated according to schedule 1, 81 per cent showed relapse within ten months; of forty-seven treated according to schedule 2, 60 per cent showed relapse within nine months; of eighty on schedule 3, 45 per cent had relapses within six months. Further data concerning the patients in the series are tabulated.

Nine cases of asymptomatic and three of symptomatic neurosyphilis were included in the study, and eight cases of pregnancy. Three nonsyphilitic infants were delivered from mothers who received only 60,000 units of penicillin, and one syphilitic infant was delivered from each of two mothers treated by each of the other schedules.

Since lesions healed rapidly and positive dark fields became negative under the small treatment given in this series, the authors emphasize the need for careful scrutiny for hidden early syphilis in all persons treated for gonorrhea with penicillin.

In contrast to the findings of certain studies that resistant strains of spirochetes are produced by insufficient treatment, the relapses in this series responded to retreatment with 1,200,000 units as readily as did untreated syphilis.

The authors conclude that the optimal dose of penicillin for early syphilis is still unknown but that a dose of 1,200,000 units gives more satisfactory results than either of the other three schedules tried.

### Treatment of Early Syphilis with Penicillin

Ross, Nelson, Lourie, and Collier<sup>6</sup> report the preliminary results obtained in five patients with early syphilis who were treated with penicillin and observed

for nine months. The patients selected were strongly seropositive and had well-marked secondary lesions.

The dosage schemes employed were (a) 30,000 units of *penicillin* given intramuscularly at 3-hour intervals for 80 injections (a total of 2,400,000 units over a 10-day period) in 4 patients and (b) 30,000 units intramuscularly every hour for 40 injections (1,200,000 units in 40 hours) in 1 patient.

Lesions and rashes cleared up within one or two weeks. There were no toxic reactions.

Of the 4 patients receiving the maximum dosage (2,400,000 units), treatment was an unequivocal success in only 1. The patient treated with the minimum dosage of 1,200,000 units had a serologic relapse after 2 months' treatment.

Although the results of this study indicate that immediate response to treatment was favorable, the authors state that it is doubtful whether penicillin was as beneficial as *arsenic bismuth* therapy might have been.

It is the opinion of the authors that penicillin treatment for syphilis will not become suitable for routine civilian practice until frequently repeated injections day and night can be avoided.

### Penicillin in the Treatment of Infantile Congenital Syphilis

Platou, Hill, Ingraham, Goodwin, Wilkinson, and Hansen<sup>7</sup> give a preliminary report of the results of penicillin therapy in the treatment of sixty-nine infants for manifest early congenital syphilis.

The only antisyphilitic treatment given consisted of 60 intramuscular injections each of 16,000 to 32,000 units of *penicillin* per kilogram of body weight. The drug was given in *saline* solution at

three-hour intervals over a period of seven and one-half days. This schedule corresponds to a total dose of 1,000,000 to 2,000,000 units for an adult.

Reactions, mostly mild, occurred during treatment in thirty-four cases. One infant developed severe, nearly fatal collapse forty-eight hours after the beginning treatment; three infants died during or soon after treatment at periods of twenty-four hours, seven days, and nine days, respectively, after penicillin was started. Two others died later (five and fourteen weeks after treatment); all of these had active syphilitic lesions, were under two months of age, and were in poor general condition. Whether these deaths were due to penicillin or to syphilis is not known.

In general, the immediate response to the treatment was gratifying. If spinal fluid findings were abnormal initially, they reversed to normal within a period of eight days to six months. Of the sixty-nine infants, thirty-nine were followed from four to twelve months. At the end of twelve months, twenty-five were physically normal and showed doubtful or negative serologic tests (twenty-one negative, four doubtful). In nine of the thirty-nine, quantitative serologic titers were either stationary at moderately high levels or were declining; these infants were well. Serologic relapse occurred in five infants, and clinical relapse in two; serologic relapse occurred from three to six months after treatment and clinical relapse in six months in both instances.

Results indicate that the present schedules are not entirely satisfactory, with respect either to the total dose or to the time dose relationship. The authors suggest an increase in the total amount of penicillin given with the same time-dose relationship. They recommend tempo-

rarily a total dose of 40,000 units per kilogram of body weight. They also recommend that definite relapse, serologic or clinical, should be retreated at double the original dose, and they define a relapse as either a persistently rising serologic titer or clinical evidence of progression of the disease. In persistent positivity of the blood serologic test alone, they do not consider an indication for retreatment.

### Penicillin Treatment of Neurosyphilis

The discovery that penicillin has anti-syphilitic properties has raised utopian hopes in the minds of all those concerned with the problem of syphilis. This optimism has been particularly high among those concerned with the therapy and management of central nervous system syphilis. Because of the widespread interest and importance of the problem, a report of results obtained after one year's experience was considered in order by Prout, Rose, Trevett, Hindle, and Solomon.<sup>8</sup>

Under the authority of the Office of Scientific Research and Development, penicillin was issued to the Boston Psychopathic Hospital in February, 1944, for the study of its effect in the treatment of neurosyphilis. In the twelve months ending February 1, 1945, a total of 106 patients with symptomatic neurosyphilis were treated. However, in this preliminary report we confine our consideration to the seventy cases followed from four to twelve months after therapy. Of the total number of patients treated, seven have died. It cannot be considered that penicillin was responsible for the deaths; and since they were not followed more than four after penicillin therapy, they are not included among the seventy cases.

The great majority of patients were also given either malaria or fever cabinet therapy in approximately one half the amount generally accepted as sufficient. Penicillin was administered intramuscularly in doses of 50,000 Oxford units per injection for a total of sixty injections (three million units). The time interval of injection was varied according to a plan designed to give the maximum information. The overall clinical and serologic results of seventy cases followed from four to twelve months form the basis of the author's report.

Clinically, it is estimated that of these seventy cases, twenty eight are improved, thirty seven are unchanged, and five are worse. The greatest percentage of improvement is to be found among the forty-nine cases diagnosed as general paresis. The most striking result, however, is shown in the six cases of primary optic atrophy, in five of which there may have been arrest of visual loss.

Spinal fluid examinations reveal an immediate response of an elevation in cells and total protein in most of the previously untreated patients, followed by a general gradual reduction in cell count, total protein and, later, a decrease in the Wassermann titer. Comparison between the clinical and serologic results shows no definite correlation at this stage of followup.

From the data presented, it is believed that penicillin is an active and effective therapeutic agent for late neurosyphilis, but comparison with the serologic results of thirty patients treated by older methods indicates that there is no striking difference at this period of observation. Caution is advised in the interpretation of these results and we believe that the time has not arrived for the distribution of penicillin for general use in the treatment of neurosyphilis.

### The Prevention of Immediate Nausea and Vomiting Following the Administration of Arsenicals Intravenously in the Treatment of Syphilis

During an experience with several hundreds of patients being treated for syphilis, Seff<sup>9</sup> noted that many individuals complained of nausea and vomiting immediately after their intravenous injection of *neoarsphenamine*. Many continued to have this complaint even after *oxyphenarsine* was substituted for *neoarsphenamine*. The nausea and vomiting were severe enough in many cases to cause the patients to discontinue treatment.

The reacting patients were questioned regarding their symptoms, and all stated that the nausea and vomiting were caused by the odor and taste of the drug which was noticed immediately at the start of the injection and before it was completed. In an attempt to counteract this, such measures were tried as chewing gum, smoking a cigarette, pinching the nostrils together, smelling perfume during the injection, and abstaining from food two hours before the injection. None of these procedures proved effective.

It was then decided that temporary anesthesia of the taste buds on the tongue might, by abolishing the taste sensation, prevent reflex nausea and vomiting. To accomplish this, the pa-

tient was given, immediately before the intravenous injection, two tablets containing *ethylaminobenzoate (anesthesine)*, 0.02 gm. each, with instructions to place both tablets upon the tongue and to keep them there until they were dissolved. As soon as this occurred the patient was sent to the treatment room to receive the intravenous injection.

In no instance in which this treatment was used did the patient experience nausea and vomiting. All those previously experiencing these symptoms who received the tablets in the experimental study refused to take subsequent treatments without first obtaining the tablets. Several hundred patients have now been so treated, and in no case have nausea and vomiting occurred.

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## DIET AND DIETOTHERAPY

DEACONESS MAUDE BEHRMAN, B.S.

For years the vitamins have held our attention in the treatment of disease, but this past year has brought a rival. The use of high protein diets in diet therapy has brought out some very interesting

results. Anderson<sup>1</sup> says, "that when one stops to consider how extensively protein substance participates in the body processes, it is surprising that functional disorders do not occur more fre-

quently as a result of temporary reductions in dietary supply." Hormones needed to regulate body processes are made up of protein compounds, as well as the enzymes which are needed to digest food. The water balance in the body is maintained by plasma albumin, globulins are needed to resist infection, and hemoglobin to carry oxygen to the tissues. Growth and repair cannot possibly go on without additional protein. When the blood protein level falls below 6.5, the circulating blood cannot hold the full amount of fluid which, under normal circumstances, remains in colloid equilibrium with the plasma protein. As the water passes into the tissues, edema results, and the blood pressure will also be affected.

In diseases such as nephroses, nephritis, malignancy, or cirrhosis of the liver, loss of blood and body proteins results in the inability of the blood to form antibodies resulting in infection.

Anemia will also result from low protein intake which can be readily understood when one considers that the blood cell framework is composed of lipids and protein and the hemoglobin within the cell is 95 per cent protein substance. Anderson says, "that pernicious anemia at present is believed to be due to a lack of either of two substances, an intrinsic factor of the gastric juice, or an extrinsic factor found in meat, particularly liver." Pernicious anemic patients often present a history of long-standing dislike for meat which may possibly have contributed to the disease. He believes that one must eventually expect anemia when the protein intake is constantly below level. The reviewer warns against the use of low salt diets which contain less than 1 gm. of sodium chloride. To prepare such a diet, it must be very low in protein, and perhaps some recall the former days when so many patients with

nephritis on low salt diets developed anemia which brought their end more quickly than the kidney condition would have otherwise. A low protein diet also means inadequate intake of vitamins, such as riboflavin and niacin.

Anderson reminds us of the increased need for protein during pregnancy and lactation. Such complications as excessive vomiting, toxemia, edema, and pre-eclampsia have been found more commonly in patients having protein intakes below normal. The milk yield during lactation is favorably increased with a good protein intake. Calcium absorption is favorably increased when there is a liberal supply of protein.

Anderson tells us that a high protein diet can actually increase the absorption of calcium several fold and after absorption about half the serum calcium exists in combination with the blood proteins which, if reduced, also reduces the serum calcium and limits the transport of calcium to the growing fetus.

During diseases of the kidney, high protein diets are used extensively. Nephritis as well as nephrosis should be treated with high protein diets. Only when the kidney function is greatly reduced should a lowered protein intake be necessary. Whenever there is a urinary protein loss, it should be replaced. Seventy-five grams of protein daily plus the amount lost in the urine may be suggested as the daily intake. During the treatment of nephroses there are periods when, Anderson says, one can not predict the trends, and it is wise to keep the body protein stores at the highest level possible. The present trend in the treatment of nephrosis or any kind of kidney disease is more to correct the metabolic disturbance of the body of which hypoproteinemia is most prominent, rather than correct the pathologic change in the kidneys.

In his discussion of the treatment of liver disease with high protein diets, Anderson reminds us that for years it has been the custom to treat patients with a high carbohydrate diet. Since the liver is the organ which is concerned with protein metabolism and is itself affected by the body protein level, it does seem reasonable. When proteins are digested and carried to the liver in the form of amino acids, the liver synthesizes them into plasma proteins, albumin, fibrinogen, prothrombin, and globulin. Fatty deterioration of the liver has been found to follow a decreased body protein which may progress to permanent damage as liver cirrhosis. Cystine and methionine (amino acids) work against the deposits of fat in the liver. Methionine is transformed into choline in the body and protects and restores liver cells. Formerly it was believed that alcoholism caused cirrhosis of the liver but, since investigation has shown that in some parts of the world where alcohol is not used they still find cirrhosis of the liver, it is now generally believed that it is the poor or abnormal diet which accompanies the habit of alcoholism which leads to the disease. Toxics such as chloroform, arsphenamine, and sulfa drugs are definitely harmful to the liver, but a storage of protein acts as reparative as well as protective.

Even ulcers may come under this discussion, because it is known that ulcer lesions have been produced in rats kept on low protein diets for long periods of time. It has not been demonstrated on human beings but it has been reported frequently that a rather high incidence of moderate hypoproteinemia in peptic ulcer has been found. There is a loss of tissue in ulcer and wherever there is loss of tissue there is a need for protein. The ulcer diet is generally a high pro-

tein diet since it contains milk and eggs in abundance.

The aged person also comes in for some consideration. There is need for protein here as well as during the earlier years of life. Often because there are no teeth to chew with, soft foods are given with no thought as to the proper intake of protein and vitamins. Borden's *Review of Nutrition Research*<sup>2</sup> gives us this interesting paragraph on the rôle of nutrition in geriatrics. "The rôle of nutrition in geriatrics is only now beginning to be recognized and appreciated. Very little definite information as to the specific needs of the aging and aged—beyond what is already known concerning the requirements of the normal young adult—has accrued in the brief period during which awareness of this problem has arisen. The one certainty upon which nutritionists and physicians agree, however, is the fact that proper nutrition, beginning early in life, and possibly even in prenatal life, is an important and decisive factor in determining the rate and severity of the inevitable degenerative changes of senility. The goal of geriatrics—a goal which proper nutrition can undoubtedly bring nearer realization—is not merely to extend life, but to increase the period of man's vigor and usefulness, to make the so-called 'declining years' fuller and more productive." As Stieglitz said: "The increased longevity of man may be made an incalculably valuable advance if health and vigor be retained and the vast potentialities of the now largely discarded elderly be developed. The reward may be the dawning of a new era of intellectual conquest, for man may then live long enough to think." The purpose of having people live longer is, as Piersol and Bortz urge, "to add more life to the years rather than more years of life." Tuohy,<sup>3</sup> in his summaries

of the causes of death, has noted that nearly as many elderly people have died of broken hips as of pulmonary tuberculosis. The reviewer believes that there is no reason why an elderly person should not be able to take at least one pint to one quart of milk daily and liver prepared in a way so that it may be taken easily, at least three times a week.

Anderson brings up finally in his article the losses in chronic colitis which may be replaced by high protein diets. Fever, increased body metabolism also call for increased protein intake.

In the field of surgery there is a sudden awakening to the importance of protein intake. Protein reserve before operations is being given a great deal of thought. Lack of appetite and vomiting before operation has brought many a patient to the operating room with depleted stores of protein. Liver damage from anesthesia rarely occurs when the liver is well supplied with protein.

The war has taught us the importance of proteins in wound healing. Pulmonary edema which may accompany low blood protein predisposes to pneumonia. In extensive burns it may be helpful to supply extra protein by intravenous route because the proper protein levels of the blood aid tremendously in the treatment.

An article reported by the reviewer in the *Cyclopedia of Medicine* (1945) explains in detail how large amounts of protein may be given. It is not always necessary to eat large amounts of meat alone. If a patient is able to eat, 3 to 4 ounces of meat, 2 ounces of cheese, 1 quart of milk and 3 eggs will supply more than half of the protein, if 150 grams is ordered. High protein milk can be made up of 635 gm. of milk, 150 gm. dry milk (Dryco), and 300 gm. of egg white. One glass of this milk con-

tains twenty grams of protein. The milk may be flavored and as much as one quart a day may be consumed.

The Committee on Nutrition of the Medical Society of the State of Pennsylvania have given the most detailed and important report<sup>4</sup> of the care which should be given to the convalescent and postoperative patient. Dr. Kelly, who is the chairman of the committee, says that the convalescent period should be an *integration of surgical, medical, psychological, and nutritional technics, aimed to aid the patient in establishing and maintaining good health*, not only during his stay in the hospital but for the remainder of his life. Disease has often led to the inability to eat and loss of appetite. Good nutrition from the beginning of an illness will hasten the recovery. Kelly emphasizes the well-balanced diet. The food should be made palatable and the patient's tastes and idiosyncrasies should be considered. Faulty food habits should be corrected and given personal attention by the physician. Food should be given in a form possible for the patient to take.

Supplementary feedings are used, he says, only when the patient is unable to take food or nutrient by mouth. They should never be employed simply to surmount anorexia. They should always be regarded as temporary measures and discontinued as soon as possible.

Kelly refers to the importance of vitamin and protein therapy in the pre-operative and postoperative care of the surgical patient.

After surgery, Kelly says that the need for vitamins is increased fivefold. Therapeutic doses administered parenterally, of thiamine, nicotinic acid, and riboflavin, are advised. It will help to prevent anorexia, nausea, and irritability



which usually accompanies the post-operative state.

The serum proteins must be restored to normal. Sufficient protein and minerals may be supplied by transfusions of whole blood or plasma, supplementary feedings, and parenteral injection, but the sooner the patient is allowed to eat normally, the better.

Following are some suggestions which are given in the care of the postoperative patient:

One thousand milligrams of ascorbic acid be given intravenously daily for three days preoperatively, and 100 mg. postoperatively for a period of a week or more, depending on the type of operation. This is suggested by Hunt.

Vitamin K need be given only to the patients with delayed prothrombin time.

Vitamin A is advisable in cirrhosis of the liver, chronic nephritis, cancer of the gastrointestinal tract, peptic ulcer, tuberculosis, gallbladder disease, and short-circuiting operations on the gastrointestinal tract.

One hundred grams or more of protein should be given daily for protection.

Adequate calories is essential. These may be supplied in the form of dextrose. A minimum of 100 gm. of dextrose is necessary to prevent ketosis for the first day and 200 gm. are desired if a patient is unable to eat or drink for two or more days.

Avoid too much fat.

Two thousand to 3000 cc. of water daily should be given. Ice water should not be given because of the increased demands made on the heart.

Five grams of salt at least should be included. This can be given in the broth or fruit juices or tomato juice. Avoid overdoses of salt which may result in hyperchloremia.

The outlines presented by Kelly in the committee's study are presented here

in detail. The reviewer has been following some of them through and they prove most satisfactory. They include the nutritional care for general operative care, for the gastrointestinal operations, and for operations on the mouth and throat.

### Dietary Outline for General Operative Care

**Preoperatively**—Some form of easily digested nutrient liquid nourishment up until four or five hours prior to administration of anesthesia; administration of 1000 mg. of ascorbic acid (as sodium ascorbate) intravenously for two days, 2 mg. of thiamine, 4 mg. of riboflavin, and 20 mg. of nicotinic acid amide orally, vitamin A if indicated, and, if necessary, 1 to 5 mg. of vitamin K daily along with 0.3 to 0.65 gm. of bile salts.

**Postoperatively**<sup>a</sup>—**FIRST DAY**—No food; tap water in small amounts. Intravenous feedings should be given according to the following specifications: If patient has no fever and has not lost any water by vomiting or sweating, he should be given 1000 to 1200 cc. of 10 per cent dextrose and 500 to 800 cc. of isotonic solution of sodium chloride to satisfy the minimum daily requirement; if patient has lost a large quantity of water and salt by vomiting or sweating, 200 cc. of 50 per cent dextrose added to 3 liters of isotonic solution of sodium chloride should be administered; if oral feedings are contraindicated for several days and a protein substitute is required, the patient should receive daily intravenous feedings of 2 liters of 5 per cent casein hydrolysate 5 per cent dextrose solution. In every case the dosage should be given in two equal instalments. Administration intravenously of 100 mg. of ascorbic acid, 10 mg. of thiamine, 5 mg. of riboflavin, 20 mg. of nicotinic acid amide, and 25,000 I.U. of vitamin A if indicated. Vitamin K in doses preoperatively if necessary.

**SECOND DAY**—Tap water in small quantities. Clear nutrient liquids may be added. Oral administration of 1000 cc. of 10 per cent solution of hydrolyzed casein over the twenty-four hour period. The addition of 0.5 per cent salt improves the palatability as well as supplying the

daily requirements for salt. Carbonated beverages or fruit juices may be used as a vehicle in the absence of any contraindications. Ten per cent solution of dextrose in the form of "Cartose" or corn syrup<sup>b</sup> should be added for calories (100 gm. of dextrose, 1000 cc. of water; 30 cc. of lemon juice may be added to improve palatability). Supplements should be given of 100 mg. of ascorbic acid, 2 mg. of thiamine, 4 mg. of riboflavin, and 20 mg. of nicotinic acid amide orally, 25,000 I.U. of vitamin A if indicated, and vitamin K if necessary.

THIRD DAY—Postoperative liquid diet.

FOURTH DAY—Soft diet.

FIFTH DAY—General house diet.

(The water intake and the amount eliminated should be measured.)

### Postoperative Liquid Diet

THIRD DAY—*Breakfast*

Diluted citrus fruit juices (*i. e.*, glass orange juice,  $\frac{1}{2}$  glass water)

Strained, thoroughly cooked cereal— $\frac{2}{3}$  cup

Cream— $\frac{1}{2}$  cup

Milk—1 glass

*Dinner*

Strained cream soup—1 cup

Simple dessert

Cream—2 tablespoons

Milk—1 glass

*Supper*

Strained beef broth—1 cup

Milk—1 glass

Simple dessert

10 a. m.

Milk—1 glass

3 p. m.

Fruit juice—1 glass, or beef broth—1 cup

*Before Retiring*

Milk—1 glass

**Foods Allowed**—Lightest of foods—thin gruels, fruit juices, broths, milk, cream, plain ice cream, fruit ices, custard, junket, and plain gelatin desserts as convalescence proceeds.

This diet, scored on the basis of the sedentary male's requirements as established by the Food and Nutrition Board, supplies approximately:

Protein—59 gm. (deficient)

Fat—88.1 gm. (sufficient)

Carbohydrate—148.5 gm. (sufficient)

Calories—1730 (sufficient for diet)

Calcium—1.855 gm. (sufficient)

Phosphorous—1.547 gm. (sufficient)

Iron—7.93 mg. (deficient)

Vitamin A—4513 I.U. (deficient)

Thiamine—1393 micrograms (deficient)

Riboflavin—2754 micrograms (sufficient)

Nicotinic acid—1.8 mg. (deficient)

Ascorbic acid—85 mg. (sufficient)

Acid-base balance—50 per cent more acid than base

Fiber

Water—1407.3 cc. (only amount in food estimated)

This diet should be supplemented with 5000 I.U. of vitamin A, thiamine 2 mg., riboflavin 4 mg., nicotinic acid amide 20 mg., and vitamin C, if necessary. Iron should be added to the diet in the form of ferrous gluconate, salts soluble in acid solution of ferric hydroxide.

In addition, a source of protein should be added, *i. e.*, at least 40 gm. of hydrolyzed casein in 10 per cent solution in fruit juice or water with 0.5 per cent salt. Concentrated protein is preferable to the customary gelatin or uncooked eggs since the former is an incomplete protein and the latter have been found to be toxic in many instances. The casein hydrolysate can easily be added to the between-meal feedings. Additional calories, if desired, can be secured by the addition of corn syrup or "Cartose" and perhaps even dried milk.

**Soft Diet**—FOURTH DAY Intermediate steps between liquid and light or bland diets. Diet consists of liquids and semi liquids. Used for postoperative cases, acute infections, and some gastrointestinal conditions.

*Breakfast*

Citrus fruit juice (diluted if necessary)  $\frac{1}{2}$  cup orange juice or grapefruit juice or 1 cup tomato juice

Cooked gruel— $\frac{1}{2}$  cup

Cream or milk— $\frac{1}{4}$  to  $\frac{1}{2}$  cup

Sweetening if desired

Egg—1 (preferably simmered twenty minutes)

Enriched white toast 1 slice

Butter 1 square (2 teaspoons)

Milk 1 glass

*Dinner*

Strained soup or consommé 1 cup

Meat, fish, or poultry approximately 3 ounces

Mashed potatoes— $\frac{1}{2}$  cup

Purée vegetables— $\frac{1}{2}$  cup

Enriched white bread—1 slice

Butter—1 square (2 teaspoons); additional butter may be used on vegetables

Cooked or canned fruit or simple dessert

Milk—1 glass

*Lunch or Supper*

Cream soup—1 cup

Enriched white bread—1 slice  
 Butter—1 square  
 Egg or cheese  
 Cooked or canned fruit  
 Milk—1 glass

*Mid-afternoon*

Fruit juice  
 Hydrolyzed casein—1 to 2 tablespoons

*Before Retiring*

Milk—1 glass

**Foods Allowed**—Fruits—fruit juices, cooked fruits (without seeds, coarse skin, or fiber). If fruit juices cause gas or eructation, the juice should be diluted with water.

Cereals and cereal products—no prepared cereals.

Cereals should be well cooked.

Breads—white enriched, soda crackers.

Dairy products—milk, sweet and acid, cream, butter, cottage cheese.

Eggs—simmered twenty minutes, poached, or scrambled on top of double boiler.

Soups and broths—clear broth, beef tea, strained soup, plain or creamed.

Meat, fish, or poultry—tender chicken (no skin), fish broiled (except mackerel, herring, shad), sweetbreads, and scraped beef. Meats, etc., should be cooked or broiled.

Vegetables—cooked puréed vegetables: asparagus, peas, string beans, beets, spinach, carrots, squash.

Desserts—ices, ice cream (except chocolate or nut flavors), junket, cereal puddings, custard, gelatin, simple cakes, plain cookies.

Beverages—milk, tea, coffee, or cocoa (if permitted).

**Avoid**—Spices, vegetables of high residue (other than those mentioned), rich desserts, chocolate, fried foods, salad dressings, raw vegetables, or fruits (except the ripe bananas and citrus fruits), fruits with seeds, skins of baked apples, prunes, or apricots.

This diet, scored on the basis of the National Research Council's requirements for the sedentary male, supplies approximately:

Protein—79.25 gm. (sufficient)  
 Fat—156.8 gm. (sufficient)  
 Carbohydrate—249.9 gm. (sufficient)  
 Calories—2753 (sufficient)  
 Calcium—1.959 gm. (sufficient)  
 Phosphorus—1.998 gm. (sufficient)  
 Iron—18.79 mg. (sufficient)  
 Vitamin A—9087 I.U. (sufficient)  
 Thiamine—1500 micrograms (sufficient)  
 Riboflavin—3203 micrograms (sufficient)  
 Nicotinic Acid—6.53 mg. (data incomplete)

Ascorbic Acid—120.02 mg. (sufficient)

Acid-base balance—Approximately twice more base than acid

Fiber—2 gm.

Water—1423 cc. (amount in food only)

This diet should be supplemented with 1 mg. of thiamine, 2 mg. of riboflavin, and 10 mg. of nicotinic acid amide.

**General House Diet—FIFTH DAY—Breakfast**

Fruit (preferably citrus)

Cereal (may be omitted)

Egg

Bacon or ham—if desired

Toast<sup>c</sup> with butter

Milk, coffee, or tea

*Dinner*

Meat, poultry, or fish

Two vegetables

Salad of fruit or vegetables<sup>d</sup>

Bread with butter

Dessert

Milk

*Supper or Lunch*

1. Choose from dinner list (cheese, eggs, soybeans, or nuts may be substituted for meat)

2. Sandwich or salad

Soup or appetizer and/or dessert

Milk

**Avoid**—Fried foods, pies and pastries, turnips, cooked cabbage, cucumbers, radishes, green pepper, raw onions.

This diet supplies approximately (based on the moderately active male requirements):

Protein—101.8 gm. (sufficient)  
 Fat—118.7 gm. (sufficient)  
 Carbohydrate—318.3 gm. (sufficient)  
 Calories—2754 (sufficient)  
 Calcium—1.378 gm. (sufficient)  
 Phosphorus—2.088 gm. (sufficient)  
 Iron—20.04 mg. (sufficient)  
 Vitamin A—7691 I.U. (sufficient)  
 Thiamine—1729 micrograms (sufficient)  
 Riboflavin—2613 micrograms (sufficient)  
 Ascorbic Acid—254.78 gm. (sufficient)  
 Nicotinic Acid—7.2 mg. (data incomplete)  
 Acid-base balance—70 per cent more base than acid  
 Fiber—6.2 gm. (sufficient)  
 Water—1088 cc. (amount in food only)

### Dietary Outline for Gastrointestinal Operations

**Preoperatively<sup>e</sup>—Oral Feedings**—Few days of rest and easily digested diet. On last

day liquid nourishment (nutrient fluids) up until four to five hours prior to administration of anesthesia. Supplementation of diet daily for three days with 1000 mg. of ascorbic acid (sodium ascorbate) intravenously, 2 mg. of thiamine, 4 mg. of riboflavin, and 20 mg. of nicotinic acid amide orally, 25,000 I.U. of vitamin A if indicated, and vitamin K if necessary (1 to 5 mg. plus 0.3 to 0.65 gm. of bile salts).

When oral feedings are contraindicated (due to pyloric obstruction or other gastrointestinal conditions preventing oral intake), the patient should receive by intravenous injection daily for one or more days two liters of 5 per cent casein hydrolysate, 5 per cent dextrose solution and one liter of 10 per cent dextrose solution. This will provide 3000 cc. of water, 10 gm. of salt (the casein hydrolysate, having been neutralized, will contain 5 gm. of salt per liter), 100 gm. of casein hydrolysate, and 200 gm. of dextrose. The solutions should be injected in two equal instalments of two hours each, or even over a period of four hours, through a No. 22 needle. In the event that the patient's condition requires transfusions of whole blood or plasma, the amount of casein hydrolysate should be accordingly lessened.

Parenteral supplements should be given of 1000 mg. of ascorbic acid, 10 mg. of thiamine, 5 mg. of riboflavin, 20 mg. of nicotinic acid amide, 25,000 I.U. of vitamin A if indicated, and 1 to 5 mg. of vitamin K if necessary.

Four to five hours prior to administration of anesthesia the stomach should be thoroughly lavaged.

**Postoperatively—FIRST DAY**—First twenty-four hours or even longer, oral administration of fluids and food withheld. Intravenous feedings of two liters of 5 per cent casein hydrolysate 5 per cent dextrose solution and one liter of 10 per cent dextrose solution. The solutions should be injected in two equal installments of two hours each, or over a period of four hours, through a No. 22 needle. Administration intravenously of 100 mg. of ascorbic acid, 10 mg. of thiamine, 5 mg. of riboflavin, and 20 mg. of nicotinic acid amide, 25,000 I.U. of vitamin A if indicated, and vitamin K if necessary.

**SECOND DAY**—Fifteen to 30 cc. of water every half hour. First substance given by mouth should be water or plain tea. Administration of 2000 cc. of 5 per cent casein hydrolysate 10 per cent dextrose solution intravenously, as above, supplemented as for the first day.

**THIRD DAY**—Oral administration of 1000 cc. of 10 per cent solution of hydrolyzed casein

with 0.5 per cent salt, and 10 per cent solution of dextrose in the form of "Cartose" or corn syrup (100 Gm. of dextrose, 1000 cc. of water; 30 cc. of lemon juice may be added to improve palatability). These solutions should be given alternately every half hour for sixteen of the twenty-four hours. If the patient is unable to consume the selected amount of nutrients, the balance should be given intravenously. Supplements should be given of 100 mg. of ascorbic acid (orally or parenterally), 2 mg. of thiamine, 4 mg. of riboflavin, and 20 mg. of nicotinic acid amide orally, and 25,000 I.U. of vitamin A if indicated.

**FOURTH DAY**—Modification of liquid diet with addition of approximately 750 cc. of 10 per cent solution of casein hydrolysate with 0.5 per cent salt, and 10 per cent solution of dextrose (as for third day). Supplementation of diet with ascorbic acid, thiamine, riboflavin, and nicotinic acid amide as above, and vitamin A if indicated.

8 a. m. —Bland cereal (cream of wheat, farina, cornmeal, strained oatmeal), gruel - 100 cc.

10 a. m. —Milk - 100 cc.

12 noon—Cream soup, strained - 100 cc.

3 p. m. —Gelatin, plain with cream - 100 cc.

6 p. m. —Bland cereal with cream - 100 cc.

**FIFTH DAY** Diet supplemented with approximately 750 cc. of 10 per cent solution of casein hydrolysate with 0.5 per cent salt, ascorbic acid, the three components of the B group, and vitamin A if indicated, as above.

8 a. m. —Bland cereal with cream - 150 cc.

10 a. m. —Gelatin with cream - 150 cc.

12 noon— Cream soup, strained - 150 cc.

Melba toast ( $\frac{1}{4}$  piece) - 2.5 gm.

3 p. m. —Baked custard (2 tbsp.) - 30 gm.

6 p. m. —Rice with cream (2 tbsp.) - 30 gm.

8 p. m. —Milk with cream - 150 cc.

**SIXTH DAY** Diet supplemented with ascorbic acid, the three components of group B, and vitamin A if indicated, as above.

8 a. m. —Bland cereal with cream and sugar - 150 cc.

Egg, poached or soft cooked - 1 egg

Milk (or Postum) - 100 cc.

10 a. m. —Gelatin with cream - 100 cc.

12 noon—Cream soup, strained - 100 cc.

Melba toast ( $\frac{1}{2}$  slice) - 2.5 gm.

Butter ( $\frac{1}{2}$  square) - 5 gm.

Milk—100 cc.

3 p. m. —Baked custard (2 tbsp.) - 30 gm.

6 p. m. —Rice with cream (2 tbsp.) - 30 gm.

Melba toast ( $\frac{1}{2}$  slice) - 2.5 gm.

Butter ( $\frac{1}{2}$  square)—5 gm.

Milk—100 cc.

9 p.m.—Milk—100 cc.

SEVENTH DAY—Diet supplemented as above.

To sixth day should be added:

8 a.m.—Melba toast ( $\frac{1}{2}$  slice)—2.5 gm.

12 noon—Pudding, bland (2 tbsp.)—30 gm.

6 p.m.—Fruit purée, bland—15 gm.

EIGHTH DAY—Diet supplemented as above.

To seventh day should be added:

8 a.m.—Melba toast ( $\frac{1}{2}$  slice)—2.5 gm.

12 noon—Potato, baked or mashed (1 serving)—150 gm.

6 p.m.—Potato, baked or mashed (1 serving)—150 gm.

NINTH DAY—Diet supplemented as above. To eighth day should be added:

12 noon—Vegetable purée (1 tbsp.)—15 gm.

6 p.m.—Vegetable purée (1 tbsp.)—15 gm.

ELEVENTH DAY<sup>f</sup>—Diet supplemented as above.

To ninth day should be added:

12 noon—Cottage cheese or egg dish (2 tbsp.)—30 gm.

6 p.m.—Cottage cheese or egg dish (2 tbsp.)—30 gm.

FOURTEENTH DAY<sup>f</sup>—Diet supplemented as above. To eleventh day should be added:

12 noon—Chicken or fish (1 serving)—100 gm.

FIFTEENTH DAY—Diet supplemented as above. To the fourteenth day should be added:

8 a.m.—Orange juice—100 cc.

FORTY-SECOND DAY<sup>f</sup>—Supplementation of diet as above. To the above may be added tenderloin steak, lamb chop, tender roast beef, tender roast lamb, crisp bacon, unstrained vegetables as carrots, asparagus tips, beets, squash, string beans, and tender young peas.

## Dietary Outline for Operations on Mouth and Throat

Tube Feeding—Milk—1000 cc.

Cream, light—300 cc.

Hydrolyzed casein—22 gm.

Orange juice—120 cc.

Vegetable juice—120 cc.

Lactose—120 gm.<sup>g</sup>

Dried milk—240 gm.

This food is divided evenly among the number of feedings prescribed, usually one-half to one pint at two- to four-hour intervals. After each feeding, the tube should be cleaned.

This diet supplies approximately (scored on the basis of the sedentary male requirements established by the National Research Council): Protein—119.5 gm. (sufficient)

Fat—162.1 gm. (sufficient)

Carbohydrate—247.8 gm. (sufficient)

Calories—2972 (sufficient)

Calcium—3.582 gm. (sufficient)

Phosphorus—3.415 gm. (sufficient)

Iron—10.28 mg. (deficient)

Vitamin A—18,264 I.U. (sufficient)

Thiamine—1371 micrograms (deficient)

Riboflavin—5949 micrograms (deficient)

Nicotinic acid—10.74 mg. (deficient)

Ascorbic acid—97.54 mg. (deficient)

Acid-base balance—5 times more base than acid

Fiber—

Water—1106 cc. (only amount in food estimated)

This diet should be supplemented daily with the B group of vitamins, 2 mg. of thiamine, 4 mg. of riboflavin, 20 mg. of nicotinic acid amide, 100 mg. of vitamin C, and vitamin K, if necessary, to meet the increased demands. Ferrous gluconate (0.325 gm.) should also be administered. The soft diet and bland diet should be prescribed as soon as mastication and swallowing functions are restored.

## FOOTNOTE REFERENCES FROM THE PRECEDING PAGES

(a) Vitamin A, 25,000 I.U. daily, orally or parenterally, should be given preoperatively and postoperatively when any of the following conditions exist: Cirrhosis of the liver or other severe hepatic damage; tuberculosis; chronic nephritis; cancer of the gastrointestinal tract; pancreatic disease; gallbladder disease; peptic ulcer; and ulcerative colitis; or in case of short-circuiting operations on the gastrointestinal tract.

(b) Since most patients with a hyperirritable digestive tract cannot take concentrated sugars orally, in such cases it is a safer procedure to eliminate the sugar and for the one day have fewer calories than considered advisable.

(c) Bread is to be preferred to toast since 25 per cent of thiamine is destroyed in toasting. Whole wheat or cracked wheat breads are to be preferred, but white or rye breads are also acceptable since all white bread and flour are enriched with thiamine, riboflavin, niacin, and iron, at least for the duration of the war.

(d) Appetizer or soup may be taken instead of the salad or in addition to it.

(e) Vitamin A, 25,000 I.U. daily, orally or parenterally, should be given preoperatively and postoperatively when any of the following conditions exist: Cirrhosis of the liver or other severe hepatic damage; chronic nephritis; cancer of the gastrointestinal tract; pancreatic disease; gallbladder disease; peptic ulcer; and ulcerative colitis; or in case of short-circuiting operations of the gastrointestinal tract.

(f) The omitted days are the same as the preceding day's diet.

(g) In case of diarrhea, "Cartose" should be used.

Martin, Simonsen, and Homann<sup>5</sup>, in a report on globin insulin, bring out a dietary problem in the management of patients on this insulin. A light breakfast, lunch, afternoon nourishment, dinner, and a bedtime feeding are advisable. The carbohydrate division is best as: one sixth for breakfast, one third for lunch, one sixth for afternoon nourishment, one third for dinner, plus evening feeding. Since most diabetics find the afternoon nourishment impractical, they cannot use it, and severe diabetics cannot be controlled on one dose of globin.

Recent literature on arthritis is concerned with adequately nourishing the patient rather than omitting or adding foods for unknown reasons. Comroe<sup>6</sup> points out a common fallacy of believing that a specific diet will cure most cases of rheumatoid arthritis. There is no proof that any specific diet caused rheumatoid arthritis or that any diet cured it. The most recent treatment is the employment of "sensible high caloric, high vitamin, anticonstipation regimen, including at least several glasses of milk per day, fresh green vegetables, fresh citrus fruits or fruit juice, and adequate protein, together with other foods to make up the caloric requirements."

Davis,<sup>7</sup> in his work with the same disease, advises that the diet be "normally balanced as to its content and within the means of the individual digestive apparatus to handle it." He should have an adequate vitamin supplement if needed. If the red cell count is low, blood transfusions may be helpful.

Harris<sup>8</sup> gives us the most recent information on hyperinsulinism. At first this condition was treated by a high carbohydrate intake. The patients showed improvement at first on this type of diet because the insulin was stimulated, but gradually they grew worse. It was then found that a high fat, low carbohydrate

diet was found to give more satisfactory results. Because of obesity existing among many of the patients, the high fat diet did not prove satisfactory. The most recent treatment is the high protein, low carbohydrate diet. The diet should be worked out to meet the individual's requirements as well as possible. A tired feeling experienced by these patients between meals may be alleviated by giving at least five small feedings during the waking hours, including fruit or fruit juices as desired.

The purine-free diet which has been used for years in the treatment of gouty patients has been criticized by Escudero and Lopez.<sup>9</sup> They have found that after a period of years on this type diet, the patient may be found to suffer from a low or mild protein deficiency. They suggest that the low purine diet contain 1.8 to 2 gm. protein per kilogram of body weight.

Observations and studies on patients with tuberculosis have brought us up to date on the subject and we now know that the energy content of food is not nearly as important for the tuberculous patient as are some other food factors. Recent studies show that these patients are in need mainly of vitamin C, vitamin A, protein, and minerals. The requirements of vitamin A and C are so great, the report says, that it is impractical to plan a diet with sufficient amounts of these materials to overcome the deficiencies. There should be an abundant amount of protein. Seventy to 100 gm. per day are suggested. The tuberculous patients' needs are greater than the normal.

Vitamins are needed in greater amounts also by the tuberculous patient. Vitamin D is needed for its special rôle in calcium assimilation and metabolism. Vitamin K deficiency has been found to be prevalent among tuberculous patients.

Those in need of vitamin K are subject to severe hemorrhages. Advanced tuberculosis is usually accompanied by anemia, therefore iron is necessary and calcium and phosphorus should be given in greater amounts than normal to help in the healing process. The diet is summarized by Getz<sup>10</sup> as high in essential foods and low in carbohydrates. As soon as the person has gained approximately his normal weight, the caloric intake should be reduced without cutting down the essential foods.

Copies of a food list for tuberculous patients containing a list of reasonably priced items can be obtained by communicating with the Division of Nutrition, Pennsylvania Department of Health.

It is no longer necessary to relax standards because of cost of food. This

is interesting because so often it is believed that the cost of the diet for the patient with tuberculosis is high and cannot be met by one in moderate circumstances.

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## ENDOCRINOLOGY

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### CLINICAL ENDOCRINOLOGY

#### The Thyroid

The treatment of choice for all adenomatous goiters, with or without hyperthyroidism, and for all cases of exophthalmic goiter is surgical resection of the offending gland. The results of no other treatment can compare with the good results which follow the skilful surgical removal of a goiter.

The patient may have assumed the responsibility of permitting the goiter to remain or he may have been told "don't bother anything which isn't bothering you."

Lugol's solution should rarely be given to any patient who has a goiter unless he has the distinct understanding that this treatment is simply a form of pre-

operative preparation and consents to proceeding with thyroidectomy as soon as the ultimate improvement has been effected. The simple colloid enlargement of adolescent children is an exception to these remarks.

Hypofunction of the thyroid in its most marked state produces the syndrome of myxedema. For every patient who has true myxedema, however, there are a hundred patients who have a low basal metabolic rate without myxedema. In many instances, the low basal metabolic rate is a part of their general clinical picture rather than the cause of their trouble. Raising the basal metabolic rate of individuals who do not have myxedema may or may not produce clinical signs of improvement. Most patients with myxedema are completely relieved

of all symptoms by a daily dose of 2 grains or less (0.13 gm.) of desiccated thyroid extract. Many patients with low basal metabolic rates without myxedema require two or three times this amount and then their symptoms may not be relieved.

### The Parathyroid

**Hypoparathyroidism** — Parathyroid insufficiency usually follows the surgical removal of, or damage to, the parathyroid glands; it occurs after thyroidectomy in about 0.05 per cent of cases. There are also a few instances of spontaneous hypoparathyroidism.

The early symptoms are usually numbness and tingling about the lips. More marked symptoms are muscular twitchings and contractions, particularly of the hands and feet. Unrecognized and untreated parathyroid insufficiency may produce generalized convulsions, cataracts, laryngeal stridor, and so forth. The Chvostek and Trousseau signs are positive. The serum calcium is low; the serum phosphorus may be high.

**Calcium lactate** is effective only when it is in complete solution, and this can be accomplished only by dissolving it in extremely hot water. The amount of calcium lactate, calcium chloride, or calcium gluconate required varies with the degree of calcium deficiency; the condition of one adult patient may be well controlled with 4 teaspoonfuls a day and that of others during the acute stage may require 20 teaspoonfuls or more. Absorption of the calcium is aided by the addition of **vitamin D**. It may be necessary on rare occasions to administer calcium intravenously; this can be given in the form of **calcium gluconate** (10 cc. of a 10 per cent solution). **Dihydrotachysterol** (A.T. 10), which is given by mouth in an average dose of 1 cc. every other day, has a powerful

effect in raising the blood calcium. The greatest drawback to its administration is its expense and the danger of over-treatment if the administration is not controlled. These objections apply as well to calciferol. The use of parathyroid hormone is rarely necessary.

Most of the symptoms of hyperparathyroidism relate to disturbances in the metabolism of calcium and phosphorus. The underlying physiologic principles are not completely understood, but present knowledge indicates that the hormone of the parathyroid glands is concerned with regulation of the serum calcium and phosphorus. The serum calcium exists in two forms, the ionized form and that bound with protein. If disease has increased the quantity of the ionized form and if the serum protein is decreased, it is apparent that the total value for serum calcium might be considered to be normal, whereas actually it is increased. For this reason, determinations of serum protein should be made in borderline cases, and if the concentration is low, an upward correction must be made in the value for calcium. This probably explains why some patients who have hyperparathyroidism are reported to have normal serum calcium.

Emphasis must be placed on the extreme variation of the symptoms in different stages of hyperparathyroidism and among different patients. The symptoms, which may be divided into three groups, result from the following: (a) Chemical changes in the blood and urine; (b) involvement of the urinary tract, and (c) involvement of the skeleton. Pronounced muscular atony associated with weakness, fatigue, and constipation is found. Anorexia, weight loss, nausea, and vomiting also are encountered. Since these symptoms are not specific and are frequently found in other conditions, includ-



ing functional states, they offer little clue to the diagnosis except when they are conspicuous. Severe polyuria and polydipsia sometimes lead to the diagnosis.

Symptoms resulting from renal calculi perhaps have led to the correct diagnosis more frequently than any other symptom, and it is not unreasonable to suggest that hyperparathyroidism should be suspected in any case of stones in the kidney.

The symptoms referable to the skeleton, when present, may vary from vague or insignificant aches or pains to the marked disability and pain accompanying pathologic fractures, cysts, tumors, and deformities.

Twenty-two of their thirty-five patients were not suspected of having the disease when they entered the Massachusetts General Hospital, and the diagnosis was made in twelve cases in which characteristic changes in bone were not present and in eight cases in which only a moderate degree of hyperparathyroidism was present. Albright, Sulkowitch, and Bloomberg concluded:

The presence or absence of bone disease is not a function of the degree of hyperparathyroidism, some of the severe cases not having it, some of the mild ones having it. Patients with bone disease and high serum phosphatase levels as a rule develop postoperative hypocalcemia; other cases seldom do.

The term "borderline" has been applied to mild cases of hyperparathyroidism and refers to the degree of hyperparathyroidism, not to the symptoms. In the diagnosis of such cases, the following points may be important:

(a) The serum protein determination, so that allowance can be made for the "bound" calcium in interpreting the total calcium value.

(b) A persistently low serum phosphorus level.

(c) The calcium excretion in the urine.

(d) The composition of the stone.

(e) Repeated blood determinations.

Camp emphasized the importance of uniform, miliary, granular osteoporosis.

He stated that this mottled demineralization, which is found only in cases of hyperparathyroidism, is distinct from the ordinary type seen in cases of osteoporosis. In some regions, decalcification progresses to produce multiple cystic regions of varying size. Cysts may reach a large size and become the site of pathologic fractures. In severe cases, because of the softness of the bones, bowing kyphosis, narrowing of the pelvis, and coxa vara are common.

Once the diagnosis has been established, operation is the treatment of choice. If a tumor is found and is removed, the condition is relieved. In some cases, as is to be expected, a tumor is not found but hypertrophy of all four glands is present and subtotal resection is indicated.

### The Pituitary

**The Posterior Lobe**—The syndrome of diabetes insipidus is easily recognized. Emphasis should be given to the fact that not every person who drinks large quantities of water and who passes large quantities of urine has this disease. If there is doubt as to the existence of this disease, the question usually can be settled by study of the ability of the kidneys to concentrate urine. No case of true diabetes insipidus in which the urine could be concentrated to a specific gravity of more than 1.010 has been reported. Patients with nervous polydipsia concentrate urine normally. The treatment of diabetes insipidus is by replacement therapy, either by injecting *pitressin* hypodermically or by intranasal insufflations of powdered whole posterior pituitary.

**The Anterior Lobe**—The hormone which has had the most extensive clinical trial is the growth hormone, and yet to my knowledge no pituitary dwarf has been restored to normal height by the use of this substance.<sup>1</sup>

### Earlier Diagnosis of Hyperparathyroidism

Hyperparathyroidism is a disease which is not characterized by any symptoms of early urgency and so goes on until, when it is diagnosed, it is suspected often from the presence of fairly late symptoms and signs, such as loss of height from collapse of decalcified vertebral bodies, nerve root pain from pressure upon nerve roots by collapsing vertebral bodies, spontaneous fractures, recurring urinary stones and calcified kidneys, and by the roentgen appearance of decalcified bone or the presence of the typical osteitis fibrosa cystica (von Recklinghausen).

Hyperparathyroidism is much more common than we have hitherto thought. It is now time for everyone to realize that the early diagnosis of hyperparathyroidism is comparable with what the early diagnosis of carcinoma of the colon and rectum was twenty years ago, at which time the operability rate was so low that palliative colostomy was the usual operative procedure. If the operability rate in terms of radical removal can be increased in carcinoma of the colon and rectum to 83 per cent where it is now, similar improvement in earlier removal of hyperfunctioning parathyroid adenomas can be accomplished. It would be of value to present roentgenograms of the bone changes in cases representing both extremes of the decalcifying effects of this disease in order that one may realize how desirable it is to make early diagnoses, before completely irreversible bone changes occur.

Hyperparathyroidism is a disease in which, because of the excessive production of parathormone, calcium is extracted from the bone, producing a high serum calcium level and a high calcium urinary output, resulting in what is de-

scribed as a negative calcium balance. The prolonged effects of this negative calcium balance produce the extensive bone decalcification with fracture. Although it is true that with the removal of the hyperfunctioning parathyroid adenoma, there is restoration of parathormone production to the normal level with a normal serum calcium, it is much more desirable that the diagnosis be made at the very early stage of the disease where the undesirable demineralizing effects of a prolonged negative calcium balance have not had an opportunity to occur.

The histories of these two cases are epitomized and presented to demonstrate that if we are to make early diagnoses of hyperparathyroidism, many more early determinations of serum calcium, phosphorus, and phosphatase must be made on suspicion. If the early diagnosis of hyperparathyroidism can be made by demonstrating the typical picture of a high level of serum calcium, a low level of serum phosphorus and a high value for alkaline phosphatase, we can save many of these patients' deformities, spontaneous fractures, and disabilities that could have been prevented had the hyperfunctioning parathyroid adenoma been discovered and removed earlier, before these bone changes had occurred. It is to be remembered that even if recalcification does take place in these cases after the state of hyperparathyroidism is surgically terminated, the recalcification must often occur after irreversible bone changes, such as vertebral body collapse, round backs and chest collapse, have already taken place.

Lahey has reported three cases of intrathyroid parathyroid adenomas occurring particularly in the upper parathyroid glands on the right or the left side which are normally placed behind the upper portion of the lobes of the

thyroid gland as it rests against the larynx. One should, therefore, when operating upon patients for hyperfunctioning parathyroid adenomas, search particularly the upper poles of the thyroid for a nodule within the substance of the thyroid gland and should always turn down the upper pole of the thyroid from where it rests against the larynx by tying and severing the superior thyroid vessels and pulling the lobe away from the larynx in order to inspect behind it. In searching for a parathyroid adenoma, if it does not immediately appear in the operative field, we have frequently suggested that the inferior thyroid artery be accurately and carefully dissected from the point where it emerges from behind the common carotid artery to where it enters the gland, and that it be inspected throughout its course carefully with the Berens-Beebe magnifying loupe, to demonstrate a possible branch of the artery running from it downward toward the mediastinum, which, if it is followed, will not infrequently lead to a subclavicular, substernal or mediastinal parathyroid adenoma.

In a patient with a large parathyroid adenoma, a very considerable portion of the parathormone is being made by the hyperfunctioning adenoma, thus lessening the functional activity of the remaining parathyroid glands. Upon the removal of the large, hyperfunctioning parathyroid adenoma, the remaining glands have not the immediate capacity to produce the amount of parathormone required by the individual, but will require from one to two months in which to develop the capacity to assume this function. It is important, therefore, to remember the probability of immediate postoperative tetany and not to permit these patients to go on unsupported with calcium or A.T.-10. It is not necessary for them to go through the very trying

physical and emotional ordeal of tetanic seizures so often associated with calcium deficiency. To avoid the possibility of this occurrence, frequent postoperative serum calcium examinations should be made to foretell this impending state, and a sufficient amount of calcium or A.T.-10 administered to avoid it, gradually withdrawing this to stimulate the remaining parathyroid glands to assume their function adequately and as soon as possible.<sup>2</sup>

### Thiouracil in the Treatment of Thyrotoxicosis

There have been several reports of the use of thiouracil in the treatment of thyrotoxicosis since Astwood's important discovery of the value of this drug, but most of these have dealt with only small series of cases. Williams and Clute report on the use of this drug in the treatment of 152 patients with hyperthyroidism. The age of the patients varied from five to seventy-two years, and the thyrotoxicosis had existed for from three weeks to twenty-two years. One or more subtotal thyroidectomies had been performed in seventeen, and twenty-nine had taken iodide until less than a month before thiouracil therapy was begun. In seven instances, iodide therapy had been discontinued because of the development of an associated rash. While most of the patients had diffusely hypertrophied thyroid glands, many had nodular goiters. In twenty-three cases there were clear-cut symptoms of myocardial insufficiency with cardiac dilatation and hypertrophy, and in five there was pronounced congestive heart failure. Thirteen had varying degrees of thyrotropic ophthalmopathy or malignant exophthalmos, and two had thyrotoxic myopathy. Two patients were treated during the last month of pregnancy and

one for the first eight months of pregnancy.

Before beginning thiouracil treatment, the patient's general condition was evaluated, particular attention being paid to the degree of thyrotoxicity, the condition of the orbital structures and the characteristics of the thyroid gland. Determinations were made of the pulse rate, weight, basal metabolic rate, and sometimes the protein bound iodine of the plasma. Most of the first twenty patients were hospitalized and were studied from various points of view. However, few of the patients subsequently treated were hospitalized for more than one day, if at all.

**Treatment**—It is important to choose the optimum dosage of thiouracil, since excessive amounts will increase the incidence of the toxic effects from the drug and may increase the size of the goiter as well as accentuate the manifestations of malignant exophthalmos. On the other hand, it is desirable to use a sufficient quantity to cause a remission within a few weeks. We prefer in most cases to administer 0.5 or 0.6 gm. daily for the first two weeks, then 0.3 or 0.4 gm. daily until the basal metabolic rate has become normal, and then 0.1 gm. twice daily. After two or three months, the dosage can be reduced to 0.1 gm. daily. Since thiouracil is rapidly absorbed from the gastrointestinal tract, rapidly destroyed in the body and rapidly excreted, it would seem desirable to administer the drug at frequent intervals throughout the day.

Subtotal thyroidectomy has been performed in fifty-nine cases. The basis for choosing this treatment rather than prolonged treatment with thiouracil was (a) the existence of a very large goiter; (b) the development of urticaria or agranulocytosis during therapy; (c) factors interfering with careful observations of the

patient—business obligations, ignorance, uncooperative attitude, temperamental reactions, psychoneurosis or distant residence, and (d) request by the patient for thyroidectomy.

Thiamine was commonly prescribed, as were sedatives. Recently, brewers' yeast has been administered routinely with the hope of protecting against agranulocytosis. Most of the patients were permitted to continue with their regular work; in fact, many never missed a single day of work.

**Results of Treatment** *Thiouracil Without Thyroidectomy* Improvement in the thyrotoxicity began within a very few days after commencing thiouracil, and within three to seven weeks there was a disappearance of nervousness, tremulousness, tachycardia, hyperpyrexia, diarrhea, and hyperhidrosis. Within the first two weeks there was but little gain in weight, but it occurred rapidly thereafter. The thyroid gland in most subjects showed little change; in some it became smaller and in a few it became larger and firmer. The basal metabolic rate became normal within two to seven weeks.

With the continuation of thiouracil treatment, the clinical remission has been maintained in all cases. Since the first month or two all have remained essentially free of thyrotoxic symptoms and signs and have maintained a normal basal metabolic rate. In four cases, with thiouracil continued for approximately a year, and in one treated for six months, the drug was omitted to determine its further need. One subject has maintained a normal status for six months, and four have remained normal for two to three months. However, one had a relapse after two months. Two other patients have discontinued therapy of their own accord on three separate occasions after they had been in a remission

for about three months. Each time a recurrence of thyrotoxicosis appeared in about a month, and it required another month to gain a remission. However, patients treated for only a few weeks experienced a recurrence within two or three weeks.

With the aid of roentgenotherapy in six patients or treatment with desiccated thyroid in ten, in almost all of the 152 persons treated with thiouracil for more than four months there has been a reduction in the size of the thyroid.

Although most patients with malignant exophthalmos experienced an exacerbation soon after taking thiouracil, with the institution of desiccated thyroid each showed improvement, which was pronounced in some cases.

The twenty-nine patients who had had iodide until less than four weeks before beginning treatment with thiouracil improved more slowly than described in the previous paragraphs. It has been found that an exacerbation did not occur if the iodide therapy was continued in very small and gradually reduced doses during the first two weeks of thiouracil treatment. Nevertheless the patients previously treated with iodide required an average of about four weeks longer to obtain a remission of their disease than did patients treated with only thiouracil.

In five cases, owing to the development of toxic reactions from thiouracil, iodide therapy was instituted. It seemed to have but little effect in two cases, even after several weeks of treatment, but was satisfactory in the other three.

**Thiouracil with Thyroidectomy—**Thyrotoxic manifestations during thyroidectomy were distinctly less severe in the cases treated with thiouracil than in the cases treated with iodide. The thyroid gland tended to be more friable and to ooze more than in patients

prepared with iodide, and occasionally adhesions extended from the thyroid capsule to surrounding structures.

The postoperative course was definitely smoother than in patients treated with iodide.

Preceding thyroidectomy, the patients were treated with thiouracil for from 8 to 240 days, averaging 42 days. It soon became apparent that patients who were treated until the basal metabolic rate became normal, requiring an average of about five weeks, exhibited less reaction to the operation than ones operated on earlier.

We have recently attempted to reduce the amount of bleeding and friability of the thyroid gland by preparing the patients with iodide and thiouracil. It was found that a remission of the thyrotoxicity could be obtained as readily as though only thiouracil was used, yet there tended to be somewhat less bleeding and friability of the gland.

In the fifty-nine cases treated by thyroidectomy, thiouracil was discontinued within about five days after the operation and most of the patients were permitted to go home two days later. Follow-up studies of all patients have shown that one developed myxedema and two had a recurrence of thyrotoxicity.

The histologic changes in the thiouracil-treated glands varied somewhat, but there were rarely involutionary changes. There were usually considerable hyperplasia of the acinar cells and many papillary projections. The colloid was scant and pale. Many acini contained no colloid, and occasionally none could be found in an entire microscopic section. Aggregations of collapsed acini appeared as solid sheets of cells. There was a slight increase in interstitial tissue. Lymph follicles with active germinal centers were not infrequently seen.

When iodide therapy was given before or during thiouracil treatment usually more colloid and less hyperplasia was observed.

Determinations of the thyroxin content of the thyroid glands of patients treated with thiouracil, without iodide, showed that only small amounts were present. Thus the potentialities for a thyroid storm would appear to be reduced.

The content of thiouracil in the thyroid gland, determined in thirty-seven cases, ranged from 5 to 29 mg. per 100 gm. dry weight of thyroid and averaged 14. No relationship was observed between the concentration of thiouracil in the thyroid gland and (a) the preoperative, operative, or postoperative course of the patients or (b) the histologic changes in the thyroid gland. Moreover, the concentration was not found to be proportional to the preoperative dosage. The administration of potassium iodide to patients receiving thiouracil did not seem to affect the concentration of thiouracil in the thyroid gland.

### Toxic Reactions to Thiouracil

Of the 152 cases treated, 16 have developed untoward reactions to thiouracil, almost all of which have appeared during the first five weeks of treatment. Two patients developed agranulocytosis, 6 edema of the legs, 5 urticaria, 4 morbilliform rash, 2 allergic arthritis, 2 vomiting, 2 fever, 1 diarrhea, 1 enlargement of the submaxillary salivary glands, and 1 leukopenia without agranulocytosis. In the last 100 cases treated, reactions have occurred in only 4, the difference being due in part to the use of dosages smaller than the ones used earlier. The only complication worthy of great concern is agranulocytosis. Both of our patients recovered after being seriously ill for several days. The patients with edema, rash, vomiting, diarrhea, and en-

larged submaxillary salivary glands were permitted to continue treatment with a reduction in the dosage of thiouracil. The other patients were either operated on soon after the appearance of the complications or were treated with iodide and thyroidectomy.

**Abstraction of Discussion** Thompson, Chicago: Thiouracil does not have an important rôle as a method or preoperative preparation of the patient. With iodine and other measures we have been able to get the mortality rate in better clinics down to 1 per cent or less, and I doubt if it could be made much lower with the addition of thiouracil. About the only preoperative use is for patients in whom the disease cannot be controlled with usual measures. It will take two or three years to determine what the precise status of this drug is. It will take that length of time to determine how serious the toxic reactions really are and in how large a percentage of cases the remission remains permanent after the drug has been discontinued.

Artels, Boston: The average person with hyperthyroidism responds well to iodine treatment, and operation can be done with little risk. There remains the severely toxic patient who, even after ten to fourteen days of iodine treatment, is a serious surgical risk. For these patients, thiouracil is a most helpful drug.

The technical difficulty which the surgeon encounters in removing the thyroid glands of patients who have received thiouracil is extremely great. On opening the skin, excessive bleeding occurs and the gland is found to be extremely soft and friable. It is difficult to isolate the recurrent laryngeal nerves and the parathyroid glands which our surgeons wish to see. Iodine involutes the gland so that three weeks after its adminis-

tration subtotal thyroidectomy can be done without difficulty. Our pathologist, Warren, has shown that the thyroid glands of patients treated with thiouracil are involuted with iodine treatment. We have had only two toxic reactions, which were manifested by fever. Since thiouracil produces hyperplasia, as does primary hyperthyroidism, the possibility of obtaining a cure from this agent seems too unlikely.

Paschkis: My experience in a series of about thirty cases is about the same as that of Williams; that, after effective and prolonged treatment, one can produce a clinical cure. Whether or not the drug will be a real cure is premature to tell. I agree with Thompson that it will take several years to solve that problem. The question whether the drug has any definite indication, aside from our curiosity to gain more experience, I would answer in the affirmative. I have had several cases in which the surgeons themselves felt that for one reason or another it was not safe to operate at all. Another group of cases in which there is a definite use consists of those which have been treated for a long time with iodine. Every one of us has seen cases which have been treated for months or for a year with iodine, apparently at one time or another with good response. Then the practitioner has continued giving them iodine, and they have come to the hospital with a high basal metabolic rate, with full-fledged thyrotoxicosis and utterly irresponsive to further iodine. These cases have responded slowly but safely to thiouracil, and we were then able to subject them to surgery or to continue medical treatment. In such cases I believe that there is already today a definite place. I have observed toxic reactions in four out of thirty cases. There was no serious toxic reaction. There was no agranulocytosis.

The reactions consisted of fever, drug rash, swelling of the joints, and, in one case, a transient jaundice. All of these, including the jaundice, disappeared twenty-four hours after treatment was discontinued. At least three out of the four were in some way sensitized, so that with renewed attempts to treat them they reacted with toxic manifestations to minimal doses. It was necessary to discontinue treatment. One of the problems is to find a way of desensitizing such patients. The other problem is of a chemical nature, whether a similar compound might be found which is less toxic. I am rather skeptical, because these toxic reactions apparently are a question of drug sensitivity, and in any active drug we shall always find cases which are sensitive.

Rawson: By determining the ability of thiouracilized thyroids to collect radioactive iodine, we have demonstrated that the drug acts by blocking the iodination of the thyroid hormone. We feel that the advantages of thiouracil over iodine in preparing thyrotoxic patients for thyroidectomy are (1) that if the drug is administered long enough, the rate of metabolism can be lowered to normal or lower, thus giving the surgeon a nontoxic goiter to ablate, and (2) that the postoperative course of patients prepared for thyroidectomy with thiouracil is much milder than that observed in comparable patients prepared with iodine. Patients prepared with thiouracil and then treated with added potassium iodide have been observed to have less vascular and less hyperplastic thyroids, which as such have been less difficult for the surgeon to remove. I am in disagreement with Williams' statement that these glands become smaller. Some of the toxic effects that have been observed by other groups have been fatal. A number of our patients have

had diffuse lymphadenopathy, morbilliform rash, drug fever, and leukopenia. We have not observed agranulocytosis. A few of the cases of agranulocytosis observed by other groups have been fatal. A number of our patients have had dental abscesses develop or become activated while taking the drug. It is my impression that this drug is more effective than iodine in preparing thyrotoxic patients for thyroidectomy. A medical cure for thyrotoxicosis will, I think, have to attack the primary pathologic physiology of the disease. I do not believe that thiouracil does that any more than surgical removal of the thyroid does. However, studies of the disease made possible with this new agent have thrown considerable light on the normal and abnormal physiology of the thyroid and may thus contribute to the discovery of a physiologic cure of this malady.<sup>3</sup>

### Use of Thiobarbital in the Treatment of Hyperthyroidism

Astwood has reported that *diethyl thiobarbituric acid* (thiobarbital) has antithyroid activity similar to that of *thiouracil*.

Our initial trial use of *thiobarbital* came in October, 1944, when a patient receiving *thiouracil* developed a fever reaction, necessitating discontinuance of treatment and in whom further antithyroid therapy was thought essential before thyroidectomy. This first patient to receive thiobarbital was an extremely fragile woman, aged seventy-five, with severe hyperthyroidism of five years' duration due to an adenomatous goiter. She weighed 83 pounds (37.6 kg.) and had a basal metabolic rate of +46. A daily dose of 0.6 gm. thiouracil was started. On the tenth day after treatment was begun, fever developed and the medication was stopped. A test dose of 0.1 gm. of thiouracil was given nine days

later, with a characteristic fever reaction indicating definite thiouracil sensitivity. The patient was then given *Lugol's solution* for one month without clinical improvement. Thiobarbital was then started in the daily dose of 0.2 gm. There was slow but gratifying improvement during the following 162 days. The basal metabolic rate fell to -16, with a gain in weight of 13 pounds (6 kg.). During the last twenty-five days of treatment, the patient had a slight elevation of temperature, with generalized muscle and joint pains. These untoward symptoms slowly subsided after the administration of thiobarbital was discontinued. Thyroidectomy was then done, with the patient having a satisfactory anesthesia and postoperative course.

*Thiobarbital* has now been used at the Lahey Clinic in the treatment of twenty-eight patients with hyperthyroidism; nine patients received thiobarbital subsequent to thiouracil and nineteen received thiobarbital initially. Nineteen patients had primary hyperthyroidism and nine patients adenomatous goiter with hyperthyroidism. Twenty-one patients who had severe hyperthyroidism, four being classified as thyrocardiac, were given thiobarbital in a manner similar to our use of thiouracil preparatory to thyroidectomy. Five patients are on maintenance therapy: One patient with malignant hypertension and primary hyperthyroidism; one patient with polycystic kidneys and uremia with primary hyperthyroidism; one patient with a metastatic mediastinal tumor and primary hyperthyroidism; one patient with recurrent primary hyperthyroidism and one patient, thyrocardiac with an adenomatous goiter, who refused operation after thiouracil preparation. One patient who was fever sensitive to thiouracil received thiobarbital for only eight days, when fever



developed and treatment had to be discontinued.

**Thiobarbital** has been given to nine patients who could not tolerate **thiouracil** because of the development of fever in six, leukopenia and granulocytopenia in one, granulocytopenia in one, and swollen salivary glands in one. Of the six patients in whom fever developed from thiouracil, three tolerated the thiobarbital but one patient developed both leukopenia and granulocytopenia after eight days of treatment, and one patient developed a mild fever after prolonged administration. The two patients in whom changes in the white blood cells took place and the one patient who developed swollen salivary glands from thiouracil were able to tolerate thiobarbital until maximum preoperative treatment was obtained.

Of the nineteen patients given **thiobarbital** as initial therapy, five developed toxic reactions. One developed fever on the eighth day and one on the twelfth day; the latter patient tolerated a reduced dose of 0.1 gm., the initial dose being 0.2 gm. Two patients developed agranulocytosis, one on the fourteenth and the other on the twenty-fifth day of treatment. Moderate leukopenia and granulocytopenia (white blood cells 2200, polymorphonuclear cells 39 per cent) developed in one patient on the twenty-first day. The two patients who developed agranulocytosis were treated successfully with **penicillin**. The patient with moderate white cell changes was asymptomatic but she was also given penicillin. The white blood cells returned to normal in eight days. The four patients in whom the thiobarbital was stopped received **Lugol's solution** to complete the preoperative preparation.

Of the total twenty-eight patients (nine patients receiving **thiobarbital** after **thiouracil** and nineteen receiving

TABLE I  
REACTIONS TO THIOBARBITAL

A. Fever	Cases
(a) 12th day .....	1
(b) 8th day .....	2
(c) Fever late (after 5 months of treatment) .....	1
B. Changes in white blood cells	
(a) Leukopenia with granulocytopenia, 8th day .....	1
(b) Leukopenia with granulocytopenia, 21st day .....	1
(c) Agranulocytosis:	
1. 14th day .....	1
2. 25th day .....	1
Total.....	8

(Bartels, E. C.: J.A.M.A., 129:932 (Dec. 1) 1945.)

thiobarbital initially), eight (Table I), or 28 per cent, developed toxic symptoms. In seven patients, the treatment was discontinued; one patient tolerated a reduced dose. This percentage of reactions from thiobarbital is about three times as great as that which we observed from the administration of thiouracil, with which twenty-three reactions occurred in 196 patients or 11 per cent.

The reactions to **thiobarbital** were found to be just as prevalent on a dose of 0.1 gm. as on a dose of 0.2 gm., four in each instance. One patient, however, was found to tolerate a dose of 1.0 gm. after fever developed from the 0.2 gm. dose. With thiouracil, most fever reactions occurred on the ninth to tenth day, with thiobarbital on the eighth to twelfth day and in one case after five months of treatment. This experience with the increased frequency of reactions to thiobarbital has led to the therapeutic policy of resorting to thiobarbital only for patients who have reactions to thiouracil. In this rôle, it has been of great help.

## SUMMARY

1. Twenty-eight patients with hyperthyroidism have received *thiobarbital*, and definite and satisfactory antithyroid response was obtained in all.

2. Of nine patients in whom toxic reactions to *thiouracil* developed, seven tolerated thiobarbital, accomplishing complete relief of hyperthyroidism.

3. Eight of the twenty-eight patients receiving thiobarbital, or 28 per cent, developed toxic reactions to the drug. Depressive changes in the white blood cells were the only serious reactions. Two patients developed agranulocytosis. There was no death due to the drug.

4. The time required to control hyperthyroidism with thiobarbital was found to be the same as that with thiouracil. The antithyroid effect of thiobarbital is apparently twelve times that of thiouracil, since 0.05 gm. of thiobarbital accomplished the same result as 0.6 gm. of thiouracil was observed to accomplish. Since no side effects were observed with the smaller dose (0.05 gm.), further studies with this dose seem justified to determine its clinical effectiveness.

5. The anesthesia and postoperative course of patients treated with thiobarbital is similar to that of the thiouracil-treated patient. The combined use of thiobarbital and *iodine* produced satisfactory involution of the thyroid gland.

6. The high percentage of reactions to thiobarbital has led to the use of thiobarbital for only those patients unable to tolerate thiouracil.<sup>4</sup>

#### Fatal Agranulocytosis Resulting from Thiouracil

The use of thiouracil in the treatment of hyperthyroidism has become widespread. It therefore seems timely to point out that the drug is not completely free from harmful effects. During the course

of thiouracil therapy, agranulocytosis may have its onset without any warning and end fatally. Himsworth reported one fatal case of agranulocytosis occurring during thiouracil treatment. Astwood reported another fatal case of agranulocytosis. His patient was a man aged thirty-seven with a classic picture of hyperthyroidism. He had received 0.2 gm. of thiouracil five times a day for twenty-seven days and then 0.4 gm. five times a day for six days. On the thirty-fifth day he was discharged from the hospital only to be readmitted two days later with severe pharyngitis and a temperature of 103° F. The white blood cell count was 1100 and no granulocytes were present. Despite intensive treatment with sulfathiazole, liver extract, and pentnucleotide, the patient died seven days later. Kahn and Stock have reported a case of agranulocytic death in a diabetic patient following the use of thiouracil. Their patient received a total dosage of 30.8 gm. over a fifty-four day period. At this point, the white blood cell count dropped to 1100 with the appearance of a rash and a pharyngitis. Again, despite intensive treatment with transfusions, liver extract, and penicillin, the patient died in a diabetic coma within five days after the onset of the symptoms. Palmer, in a study of twelve thiouracil treated cases, observed the depression in the white blood cell count in two cases without a change in the differential count. In these two cases, the white blood cell count returned to normal within three days after discontinuance of the drug. Williams, in a recent review of 125 cases, observed agranulocytosis in two cases; no details are given. In a previous report, Williams and Cate observed one case of agranulocytosis in which recovery followed treatment with large doses of pentnucleotide and liver extract. Bartells, however, in a series of eleven cases,

noted no untoward effects during the course of the treatment.

This paper reports an additional case of agranulocytosis following the use of thiouracil, with necropsy.

### REPORT OF CASE

A man, aged seventy, had, for several years before the present admission, an elevated basal metabolic rate and an x-ray shadow in the superior mediastinum interpreted as a substernal thyroid. Because of the age of the patient and the technical difficulties involved, surgical removal of the thyroid was not considered feasible. He was admitted for the fourteenth time January 16, 1944. The chief complaint was weakness and extreme fatigue. The history revealed that he had lost a considerable amount of weight in spite of a good appetite. In addition, he had been suffering from persistent diarrhea and for a few days prior to admission had a productive cough and moderate chest pain.

The patient was extremely emaciated and chronically ill. He was slightly orthopneic and perspired freely. There was a fine tremor of the hands. The thyroid was not palpable. The heart was enlarged to the left, with a systolic murmur at the apex. Auricular fibrillation without pulse deficit was present. The remainder of the physical examination was entirely negative. The diagnosis of hyperthyroidism was made.

During the first five days of treatment, the white blood cell count fell from 9500 with 60 per cent polymorphonuclear leukocytes to 5150 with 65 per cent polymorphonuclear leukocytes. During the next thirteen-week period, the patient gained 31 pounds (14 kg.). All gastrointestinal symptoms had disappeared. His basal metabolic rate dropped from plus 40 to plus 2. The pulse rate dropped from an average of 100 to an average of 80. The tremor disappeared. His weight of 97 pounds on admission rose to 124 pounds (56 kg.). The white blood cell count during this period ranged from 5100 to 7400. He was then placed on a maintenance dose of 0.9 gm. daily of thiouracil and discharged to the outpatient department on the one hundred and thirty-first hospital day.

He was followed in the clinic from May 29 until July 3, 1944. During this time he remained asymptomatic and maintained his weight at 124 pounds. He was kept on 0.9 gm. of thiouracil once a day for twenty-nine days. Then the dosage was cut to 0.6 gm. daily for seven days. On July 3, a white blood cell count was taken and

was found to be 150, with 37 per cent polymorphonuclear leukocytes. He was immediately admitted to the hospital.

The patient felt well for the first two days. His temperature then began to rise and on the fourth day was elevated to 105° F. On the fifth day he was noted to have an inflamed pharynx. The temperature continued to be elevated and his pharyngitis progressed in severity. He died on the seventh hospital day. During this period the white blood cell count continued to fall and was 450 without any granulocytic cells on the day of death. Pentnucleotide given intramuscularly and blood transfusions were of no avail. He had received 113.6 gm. in 128 days.

Following the transfusion, his temperature became elevated. Penicillin was administered during the last twenty-four hours without any effect on the temperature or course.

*Postmortem Examination* (performed forty-eight hours after death)—The pharynx was intensely congested and reddened. The thyroid had a normally situated left lobe which was slightly smaller than normal. The isthmus was unchanged. The right lobe was found to be entirely within the apex of the right chest and compressed the apex of the lung downward. It was five times the usual size and coarsely nodular, with the nodules ranging in size from 2 to 4 cm. in diameter. Some of these nodules contained calcium and bone formation, while others were hemorrhagic and necrotic. Large follicles of colloid were visible on section. The trachea was not compressed. The left lobe had a smooth surface. On section, it presented a fine, honey-chambers appearance.

**Comment**—The dosage given in this case is somewhat higher than that which is generally used at present. It was problematic, however, whether the total dosage was related to the onset of the agranulocytosis. It is thought that this complication occurs on the basis of developing sensitivity or idiosyncrasy rather than on the cumulative effect of the drug. In relation to this, Williams, in an analysis of two cases treated with thiouracil, in one of which death occurred of cerebral hemorrhage and in the other of bronchopneumonia, found that the highest concentration of the drug was in the adrenals, pituitary, and bone marrow.<sup>5</sup>

### Extrathyroid Effects of Thiouracil Therapy

Thiouracil, a derivative of thiourea, exerts a powerful depressant action on the production of thyroid hormone and hence has been applied clinically to secure reduction of the basal metabolic rate in thyrotoxic patients. During the past twenty-one months we have used thiouracil in the treatment of a series of ninety-six patients with hyperthyroidism, which in many of the patients was complicated by other conditions and, in addition, there were several who were reluctant to undergo a second operation for recurrent hyperthyroidism. They have been much impressed by the favorable effect of the drug on these extrathyroid complications caused by the heightened basal metabolism or by a disturbance of glandular equilibrium, or both. As the basal metabolic rate fell, they observed a high degree of amelioration in the cardiac sequelae, great lessening of the associated diabetes, decrease in exophthalmos and improvement of the psychic state. They have encountered a much higher incidence of granulopenia, about 20 per cent, including one case of typical agranulocytosis.

In general, the dosage was 1 gm. daily for three days, followed by 0.6 gm. until the basal metabolic rate dropped to within normal limits, approximately  $\pm 10$  or less. In every case in which more than 0.2 gm. was administered daily, it was a fixed rule that a white blood count had to be made every three days, and a differential count, if there was over 20 per cent drop in the total number of leukocytes. When the maintenance dose was reduced to 0.2 gm. or less and the leukocyte count remained within normal limits, 0.2 gm. daily was given for one week, no medication for the second week, and 0.2 gm. daily for the third week.

A blood count was then made. This method reduces the necessary blood counts to one every three weeks and sufficient thiouracil is administered to maintain the basal metabolic rate within normal limits. There were no restrictions put on the patients, who were freely ambulatory.

The first response was subjective. After seven to ten days, the patients stated that they felt calmer. With lowering of the basal metabolic rate, there were objective signs of loss of agitation, decreased perspiration, decrease to loss of tremor and disappearance of diarrhea. It was striking that there was a lag in the slowing of the pulse and in the gain in weight, particularly the latter. In some cases there was even a slight loss of weight during the first weeks of active treatment, but following this there was a gradual gain, amounting in one case to 55 pounds (25 kg.). In many cases loss of tachycardia did not occur until a considerable period after the drop in basal metabolic rate. One patient developed granulopenia on the eighty-fifth day of therapy, while the white count of another patient dropped from 8100 to 4400 thirty-six hours after taking the drug.

It is well known that diabetes associated with hyperthyroidism is difficult to control. Improvement in the diabetic status goes hand in hand with improvement in the thyroid status. This has been frequently demonstrated by thyroidectomy and iodine. As would be expected, thiouracil yields similar results. As in cardiac patients, it would seem preferable to accomplish such a result by medical rather than surgical means, since the risks of anesthesia and operation can be avoided.

Sixteen per cent of our patients were in sustained remission with no medication whatever for periods ranging from

over two months to fifteen months after discontinuance of the drug. In 20 per cent, thiouracil had to be discontinued because of sensitivity, and nine of these were submitted to surgery without any untoward finding at operation. In fact, this drug is an excellent means of securing the lowering of the basal metabolic rate requisite for operation without necessitating any preliminary period of rest. There were twenty-five cases (26 per cent) in which the basal metabolic rate rose as soon as the maintenance dosage was lower than 0.2 gm. daily. These had blood counts every three weeks, as outlined.

The results would seem to indicate that thiouracil will bring about a drop in the basal metabolic rate in all patients suffering from hyperthyroidism. It has, however, serious toxic effects and the patient must be kept under continuous medical observation so that the drug may be promptly discontinued and further injury to the patient prevented. The main danger is agranulocytosis, and since we have noted a definite and sudden granulopenia in 20 per cent of our patients, it is apparent that a white blood count must be done every second or third day, and the drug must be stopped instantly if there is a sudden drop in the total leukocyte count, or if the granulocytes drop below 45 per cent. If there is a sudden rise in temperature, accompanied by arthralgia, myalgia, lymphadenopathy, or the appearance of a rash, the drug must be discontinued. It is well to instruct the patient to inform any physician called in of the medication being taken so that sulfonamide drugs or other compounds containing the benzene ring are not prescribed. The patient should be given only two or three days' supply, just enough to last until the next blood count. Since this drop in the white count can occur with discon-

certing suddenness at any time, it is doubtful whether thiouracil is as yet ready for long-continued use in routine medical practice, until some method of protecting the bone marrow is perfected. The use of pyridoxine, vitamin B, in prophylactic doses of 150 mg. daily by mouth, or 200 mg. intravenously where a severe drop in the leukocyte count has taken place, seems at present to be most promising.<sup>6</sup>

### **Myxedema Following Iodine Administration for Goiter in a Girl Aged Six Years**

The administration of iodine to a patient with simple colloid goiter causes little change in the size of the gland and usually no alteration of physical signs or symptoms. Webster stated that in such cases a transitory rise in metabolic rate occurs, but nothing of clinical significance.

In earlier years iodine was used for colloid goiter, but the paucity and uncertainty of results have caused us to abandon this practice. If, however, there is a coexistent hypothyroid state, the administration of desiccated thyroid will not infrequently result in a marked reduction in the size of the goiter, in some cases returning almost to normal, although on palpation the gland feels pebbly or slightly nodular.

The use of iodine in the prevention of colloid goiter is an accepted fact and would tend to show that colloid goiter is due to iodine lack. Marine's original conception of the cause of colloid goiter being due to intermittently recurring hyperplasia and involution as a result of iodine lack, bringing in the play of the pituitary thyrotropic hormone, is received favorably by most writers. The process might be reversible if iodine is supplied early in the cycle, but when the colloid type of goiter becomes estab-

lished, iodine will not restore the gland to normal. We do see large colloid goiters with myxedema, suggesting hyperplastic areas either before myxedema occurred or even coexistent with it. Administration of desiccated thyroid in such cases supplies the bodily demands for thyroid hormone, probably causes involution of the hyperplastic areas and possibly some inhibition of pituitary thyrotropic hormone.

Surgical removal of colloid goiters does not always end the process of enlargement as they recur occasionally, perhaps more than occasionally. In a few cretinous children with large goiters, recurrence may take place even when they are supplied postoperatively with adequate doses of desiccated thyroid. In one such case, a recurrence took place with severe hyperthyroidism, and we have recently seen a cretinous child with goiter develop hyperthyroidism spontaneously.

Administration of iodine to patients with the hyperplastic gland of Graves disease is followed by evidence of decreased output of thyroid hormone, the gland in this disorder being particularly well drained of iodine. Myxedema or states of hypothyroidism approaching gross clinical myxedema have been seen in cases of Graves disease following iodine administration. We have noted them particularly in early recurrent cases when small hyperplastic thyroid remnants were present which, being in themselves overactive, cause a minimum of clinical signs and only slight elevations of metabolic rates. When iodine is administered in such cases, thyroid deficiency may develop, as shown by the basal metabolic rate, cholesterol and physical findings, although it is far from a frequent finding. Proger and Brauns reported a case in which iodine relieved hyperthyroidism, following which myxedema ap-

peared, so that desiccated thyroid was given to correct the myxedema. A normal balance was maintained by giving continued doses of each.

The cases reported are unusual from the standpoint of therapeutics as well as providing a curious link in the chain of thyroid physiology. It appears to be the first instance we have seen of the production of myxedema in a child who was thought to have a simple colloid goiter. In view of the resulting myxedema, the logical conclusion is that hyperplasia existed without clinical hyperthyroidism. While it is tempting to assume that a mild hyperthyroidism followed recovery from myxedema, and that this occurred because there was not adequate inhibition of the pituitary by thyroid hormone, the evidence does not justify this conclusion. It does, however, lend support to the possibility of pre-existent subclinical hyperthyroidism.

### CASE REPORT

The patient was a six year old girl in whom a small enlargement of the thyroid was noted by her mother in June, 1943. There were no other observed signs or symptoms shown and there had been no weight gain for eight months. A basal metabolic rate was reported as -11. Lugol's solution, 5 drops twice a day, was given. On August 4, 1943, a second metabolic rate of -21 was obtained. The patient gained 7 pounds, complained of feeling cold, and became mentally sluggish. On August 18, 1943, when she was first examined at the Clinic, there were puffiness of the face and pallor. The thyroid was slightly enlarged and felt like a hyperplastic gland of hyperthyroidism. The child's mother stated that the swelling in the neck became larger after taking iodine. The pulse rate was 76 and weight 61 pounds. Blood cholesterol was 432 mg. per 100 cc. Iodine was discontinued.

When seen again on September 29, 1943, the patient weighed 60 pounds, pulse rate was 104, and the thyroid felt somewhat smaller. Blood cholesterol was 179 mg. and all evidence of myxedema had disappeared. Because of the pulse rate and the type of gland, the question

of hyperthyroidism was entertained but not felt likely. There were no other concomitant signs or symptoms.

**Summary**—A child of six with a small goiter, thought to be colloid type, was given Lugol's solution, following which myxedema developed. With an initial metabolic rate of —11 per cent, it would ordinarily seem unlikely that hyperthyroidism had been present, yet weights obtained at school revealed a failure to gain weight for the previous eight months. This fact suggests hyperthyroidism with a normal metabolic rate. The response to iodine is more consistent with that possibility than with simple colloid goiter. The patient appears well now and the thyroid gland on palpation has the consistency of ordinary colloid goiter.<sup>7</sup>

### Some Misconceptions and Abuses in Gynecologic Organotherapy

Novak states that a very substantial proportion of the work of the gynecologic specialist has to deal with endocrine disorders of one form or another. This proportion, as a matter of fact, is considerably larger than that represented by patients needing surgical procedures.

A considerable fraction of the practice of every general practitioner likewise has to do with the various functional disorders of women. The subject of endocrinology is a very fluid and expanding one, demanding a special interest which the practitioner may not possess or for the development of which he does not have time. Small wonder, therefore, that he so often takes the short cut of turning to the literature of manufacturers for simple and not always conservative expositions of endocrine therapy for gynecologic functional diseases.

Every practitioner should know that the ovary produces two hormones, estrogen and progesterone, and that these are

very tangible and well understood chemicals which can be prescribed as he prescribes the better understood drugs. He should know the pharmacologic effects of these hormones, especially upon the uterus, also, that the production of these hormones by the ovary is made possible because of the underlying influence of the anterior pituitary, through the agency of the gonadotropic hormones. One of these, the follicle-stimulating hormone (F.S.H.), brings about maturation of ovarian follicles and thereby the production of estrogen; the other, the luteinizing principle (L.H.), brings about luteinization and corpus luteum formation and thereby the production of progesterone. He should understand, however, that the pituitary sex hormones, unlike those of the ovary, have not been isolated in pure form, that no one knows their chemical composition, and that no commercial preparation of these hormones has established itself as of definite therapeutic value.

He ought to know, too, that the anterior pituitarylike hormones found in the blood and urine of pregnant women and animals are not really pituitary principles; they are produced in the embryonic trophoblast, so they are properly spoken of as chorionic hormones. Furthermore, he should know that this hormone produces little or no effect upon the human ovary, so that he would not, for example, wish to employ it in the treatment of amenorrhea. He ought also to know that the chorionic hormone found in the blood serum of the pregnant mare is dominantly follicle stimulating in its effects, that its effect on the human ovary is at least questionable, and that its extensive employment in recent years has yielded results almost universally disappointing.

He should, furthermore, recognize that male sex hormone principles are to

be found in the blood and urine of all women during menstrual life, that they may play some as yet unknown part in the cycle, and that, while possibly produced at times by the ovary, they probably have their chief source in the adrenal cortex. He should be familiar with the assumed rationale of androgen therapy in certain menstrual disorders, as well as with its possible hazards.

Finally, he should appreciate that the thyroid is in some unknown fashion linked up with the gonads, and that its employment, even though it frequently is more or less empiric, is often justified by the clinical results which it yields.

The most frequent and the most clearly defined indication for estrogenic therapy is furnished by the vasomotor symptoms of the menopause. The indication for estrogenic therapy is not the menopause *per se*, but the characteristic menopause symptoms only when and if they occur and when they are sufficiently severe to need any treatment at all.

A common failing is to attribute to the approaching menopause almost any general nervous symptoms exhibited by women over forty. There is no way of predicting in a woman of the early forties who has often been told that "the change of life is beginning to work on her" whether she will actually pass through the menopause within the next year or two or perhaps not for ten years. To put such a woman on estrogen therapy is unsound and even harmful.

Another extremely common abuse is to put menopausal patients upon a more or less fixed dosage of estrogens, often kept up indefinitely. The menopausal endocrine readjustment is bound to take place whether or not we resort to endocrine therapy, and the only need for the latter is to give symptomatic alleviation

to the patient when and if the symptoms become troublesome.

Almost always the vasomotor phenomena are intermittent, and it is only during these exacerbations that treatment is necessary.

When the natural estrogens are administered hypodermically, as they still often are, it is especially unwise to let the patient acquire the idea that she needs regular injections once or twice or thrice a week in order to avoid symptoms.

Even worse is the doctrine of prophylactic estrogen therapy, oral or hypodermic. The fact that it produces unpleasant, though not dangerous side effects, has led to the introduction of other similar nonhormonal estrogens, such as hexestrol, as well as preparations of conjugated and synthetic estrogens. What has been said as to possible abuses of estrogen therapy applies to these orally administered substances as well.

The chief hazard of such injudicious dosage is that it not infrequently produces uterine bleeding in women who had ceased menstruating many months or perhaps several years previously.

The next most frequent field for estrogenic therapy has been in the treatment of amenorrhea, admittedly one of the most unsatisfactory problems in gynecologic organotherapy. By way of digression, attention may be called to the fact that substitutional therapy is not necessarily disgraceful *per se*, as some would appear to believe. The employment of insulin in diabetes or of thyroid substance in hypothyroidism are but two of many instances in which substitutional therapy is highly beneficial or even life-saving. It is quite probable that in at least some cases of amenorrhea the supplementary employment of estrogens may be helpful. The fact remains, however, that in the great majority of cases of



amenorrhea the most that can be expected from either the natural estrogen or stilbestrol is the artificial production of a pseudomenstrual bleeding which will not recur unless the treatment is regularly repeated. Furthermore, such treatment does not in any way enhance the patient's chances for pregnancy in that large group of cases in which the real target of treatment is the sterility so often associated with the amenorrhea.

Still another common fault is the too frequent resort to estrogens in the case of young girls of perhaps fifteen or sixteen years of age simply because they have not yet begun to menstruate. There are quite a number of girls in whom the first menstruation does not appear until sixteen or after, and unless there is some obvious endocrinopathy, direct ovarian therapy before the age of sixteen is rarely justifiable.

**Progesterone Therapy**—The chief indications for progesterone therapy have been in the treatment of functional bleeding, primary dysmenorrhea, and threatened or habitual abortion. I have no criticism of the plan, which has appeared to be based on fairly good scientific evidence, but I confess that I have not been as convinced of its value as have many other clinicians. The problem is not an easy one to study, as it is impossible to apply the principle of scientific control.

Many women who bleed in early pregnancy go on to full term without progesterone, and many abort who are heavily dosed with it. Embryologists agree that the most important cause of early spontaneous miscarriage is a defective germ plasm, and there is no evidence to indicate that this is influenced by progesterone. If, as is probably sometimes the case, the nidation of a normal egg is imperiled because of a real progesterone deficiency, treatment would obviously be more rational, but

there is no sure way of predetermining this. In the present state of the problem, most of us would feel culpable if we did not include progesterone in our treatment of threatened or habitual abortion, but it remains for the future to reveal how much benefit actually accrues to the patient.

**Gonadotropic Therapy**—There is no effective preparation available of the pituitary sex hormones themselves, but there is widespread use of the gonadotropic principles of pregnancy urine. Many practitioners have the idea that in using pregnancy urine preparations, they are employing pituitary principles, and that they have a stimulating effect upon the ovaries. This would seem to be the only explanation of their widespread use in amenorrhea, practically always without success. As a matter of fact, there is fairly general agreement that the pregnancy urine hormones, formed by the embryonic trophoblast and not by the hypophysis, have practically no effect upon the human ovary.

Another gonadotropic preparation which has been much abused is that made from the serum of the pregnant mare. This principle is dominantly follicle ripening in its effect, certainly in the ovaries of experimental animals, and possibly at least on the human ovary, though this has not been established beyond doubt.

Even in the so-called anovulatory type of sterility, in which there would be at least some indication for such therapy, the results have been increasingly disappointing.

**Androgenic Therapy**—Testosterone propionate preparations have achieved wide vogue in the treatment of primary dysmenorrhea and functional bleeding. For this general plan, there can be no criticism, in view of the notorious inadequacy of all of our methods of treatment

of this troublesome disorder when it involves women of the younger age group, and the fact that it not infrequently brings about genuine amelioration of the bleeding. The abuse in its use comes in the excessive dosage often employed, though probably less so than formerly, since there has been such wide publicity of the possible hazard of producing masculinization effects. It is becoming increasingly recognized that in order to avoid such highly undesirable effects, the dosage must be kept low, and it is probably safest to avoid a total monthly dosage of more than about 200 mg. With such a low dosage, there is practically no risk of unpleasant sequelae.

**Summary**—This paper is devoted to a discussion of certain misconceptions, errors, and abuses in the employment of endocrine preparations in the treatment of various functional disorders of women. A prerequisite for intelligent endocrine therapy is at least an elementary knowledge of reproductive physiology. The estrogenic treatment of menopausal symptoms offers a good illustration of some of these abuses of hormone therapy, such as the too quick and often unnecessary resort to estrogens, the prescribing of fixed or "prophylactic" dosages, etc. The present widespread use of diethylstilbestrol has also brought with it some abuses, at times distinctly harmful to the patient. Other subjects briefly discussed are certain misconceptions and limitations in the endocrine therapy of amenorrhea, dysmenorrhea, and functional bleeding.<sup>9</sup>

### Priapism in Leukemia

True priapism is a pathologic erection of the penis characterized by persistence, pain, and absence of libido.

**Etiology and Pathology**—The etiology of priapism in leukemia is nervous and mechanical. Postmortem studies have demonstrated that whatever the

exciting cause, the persistence of priapism was due to a mechanical factor, which proved to be a leukemic thrombosis in the corpora cavernosa and dorsal veins of the penis. The glans was seldom involved in the process.

**Treatment**—Priapism persisting for forty-eight hours or longer and associated with leukemia is treated by deep x-ray therapy.

### SUMMARY

1. In persistent priapism, the presence of leukemia must be considered.
2. Priapism occurred as a complication of leukemia in only 0.65 per cent of the 309 cases in men seen in this clinic. However, it occurred in 3.2 per cent of men with chronic myelogenous leukemia.
3. The cause of priapism may be nervous in origin, but the persistence is undoubtedly due to thrombosis in the venous spaces of the corpora cavernosa.
4. Deep x-ray therapy given systemically for treatment of the leukemia and locally for the treatment of the priapism is the therapy of choice.<sup>10</sup>

### Fulminating Meningococcemia (Waterhouse-Friderichsen Syndrome)

The Waterhouse - Friderichsen syndrome is designated as a symptom complex characterized by purpura and shock associated with the postmortem findings of bilateral adrenal hemorrhage. Karsner states that this syndrome may be caused by the streptococcus, pneumococcus, or influenza bacillus. Boger cites a case in which meningococci were demonstrated by direct examination of the peripheral blood smear. He states this finding has been recorded as occurring only in fatal cases.

The most common symptoms they record are headache, vomiting, gastrointes-

tinal symptoms, fever, chills, abdominal pain, general pain over the entire body, cyanosis and ecchymotic and purpuric spots varying in size from small petechiae to large areas, often confluent and forming a maculopurpuric rash over the body. The skin lesions may develop over the body even while the patient is being examined. The patient becomes rapidly worse in a few hours and soon becomes mentally confused, delirious, and moribund. Frequently, the pulse is imperceptible but may reach 200. The blood pressure may drop to 60 or 50 in a short time. The leukocyte count recorded in five cases ranged from 20,200 to 99,500. Positive blood culture was present in only a few cases. In five of these nineteen cases, intravenous injections of sodium sulfadiazine and dextrose were given with no apparent change in the course of the disease. Intravenous saline solution and adrenal cortex extract were tried in five cases with no apparent result. There was massive hemorrhage of the adrenals in all the typical cases. They stated that bullous lesions with necrosis of the skin were reported and gangrene of the toes or the whole extremity may occur rarely. Bernstein cited only one case in the literature in which gangrene of the toes or caudalgia accompanied meningococcic meningitis.

In the report made by Martland in February, 1944, he states that the Waterhouse-Friderichsen syndrome is apparently that of a fatal infection with a duration of from eight to forty-eight hours from the time of onset, that it is doubtful whether any patient recovers and that death is due to an overwhelming meningococcic infection rather than to insufficiency of the adrenal cortex.

Herrick believes that the meningococcic infection has a selective affinity for the delicate capillary endothelium of the adrenal. Cosgriff as late as August,

1944, suggested that penicillin might prove valuable for the treatment of this condition.

### CASE REPORT

A white woman aged twenty-seven, awakened on August 22, 1944, with a slight sore throat. At dinnertime she had a slight headache and at midnight she began to vomit and complained of pain over the body, especially in the abdomen. About 4 A. M., the patient was still vomiting a little; she had pain in the abdomen but there was no definite localization of pain or rigidity. The tenderness was about the same over the left kidney area as over any other part of the abdomen. There were no marks on the body anywhere at this time, which was about 4 30 in the morning, or about four and one-half hours after the onset of the illness. She complained of pain on motion or pressure over the extremities and abdomen. She appeared dazed or mentally confused, answering questions slowly and hesitatingly, and no definite source of the manifest toxicity could be determined.

When the patient reached the hospital there was an extensive eruption over the body. Later the sister said that, from the time she went to make the call until she returned to the patient, the purpuric spots had increased noticeably. The purpuric spots began to appear about 5 A. M., starting on the right thigh and extending distally with great rapidity. She stated that these spots "popped out just like corn popping." At 9 A. M., the purpuric blemishes of varying size were very extensive over the body; only a few small petechiae appeared on the face. On the knees, legs, and feet there were many large areas with what appeared to be thrombotic centers. Both the great toes and several of the small toes seemed almost gangrenous at this time. At the dorsal area of each foot a purplish discoloration extended proximally from the base of the toes.

The patient had a slightly loose stool. Sulfaguanidine was started at once. Because of the rapid progress of the disease, penicillin was administered, 20,000 units of the substance injected intramuscularly at about 9 A. M. and ordered to be given every four hours. The pulse and temperature were about normal when the patient was seen at her home. Soon after arriving in the hospital, the temperature rose to 102° F. and the pulse rate to 136. Approximately three hours after the second dose of penicillin had been administered the temperature dropped to 99° F., the pulse rate to 80. A

leukocyte count was 9600; the urine and blood were within the limits of normal.

About midnight the pulse was weak and irregular and the patient was restless, was confused, and complained of pain in the extremities. Her feet and legs were cold and clammy.

The blood pressure had now dropped to 60 and at times was almost unobtainable. After several attempts were made to give intravenous glucose without satisfactory results, an ampule of ephedrine was given. About fifteen minutes later the fluid flowed in freely. From this time on not much difficulty was encountered in giving intravenous solutions. At this time adrenal cortex extract was given. The leukocyte count had risen to 47,000 on the second day.

On the third day the patient began to bleed from the nose and the vagina. This was about two weeks from her normal menstrual period. The bleeding was not excessive, but 3 cc. of a hemostatic was given. The external bleeding stopped promptly. The patient showed some improvement from the third day on, and on the fifth day there was a decided improvement in her general condition. Several toes were now definitely gangrenous, and many large ulcerated areas were present on the knees, legs, and feet. The only one located above the knees was on the right buttock. The temperature rose to 103° F. at this time. This was probably due to the infection in these gangrenous areas.

Large wet antiseptic packs were ordered to gangrenous parts. The temperature then came down quite promptly. These packs were put on for forty-eight hours and then removed, to be replaced as soon as the temperature began to rise again. The purpuric spots on the arms, hands, and upper part of the body faded gradually, leaving small, purplish spots. Over a period of several days the necrotic areas were cut away from the centers of many of the large ulcers. Penicillin and sulfaguanidine were discontinued on the eighth day after the patient had entered the hospital. One month later she was taken to the operating room and given spinal anesthesia, and the following toes and fragments of toes were removed: The great toe on the right foot, including the distal end of the metatarsal bone; the distal phalanges of the fourth and fifth toes of the right foot; the great toe of the left foot except the proximal phalanx, and all of the third and fourth toes of the left foot. The wounds were all closed fairly tight and healed with but little further removal of tissue. Two weeks later, the patient walked with a pair of improvised shoes. At the end of

four weeks following the operation, she drove her car to the office. The general condition of the patient is good and she walks with very little impairment in her gait.

**Conclusion**—It is impossible to state definitely that any case presents all of the symptom complex of the Waterhouse-Friderichsen syndrome of meningococcic type unless an autopsy is made. The external signs and symptoms seem to place this case in this class. The administration of penicillin perhaps accounts for the favorable result.<sup>10</sup>

### Hypertrichosis and Myxedema

The occurrence of an increased amount of hair, coinciding with the onset of myxedema and its loss after treatment with desiccated thyroid, is unusual.

### CASE REPORT

A twenty-eight-year-old unmarried woman who was first admitted on June 7, 1943, complaining of shortness of breath of one year's duration. The shortness of breath had been so distressing that the patient could not walk any great distance without its occurrence. In cold weather, she had to stop walking after half a block, because of the constriction in her chest. She also complained of some vague joint pains, swelling of her feet, and puffy enlargement of her hands. Her mental reactions were retarded, her skin was dry, she was always tired and felt cold all the time. About two years previously, she had periods of amenorrhea or very slight flow. Her weight had increased from 124 to 147¾ pounds.

The skin and the hair on her head were quite dry. The hair on her arms was normal or slightly increased over the average, and the pubic hair was plentiful. There was a marked increase in the amount of hair on the side of her face, with long hairs around the chin, neck, and upper chest. The skin showed areas of pigmentation, but not the mucous membranes. Pitting edema was present in the lower extremities. The heart sounds were of a fair quality. The blood pressure was 110 mm. systolic and 70 mm. diastolic, pulse 70, weight 145 pounds, and height 62½ inches.

The blood examination showed a hemoglobin of 92 per cent, red blood count 4,500,000, and

white blood count 10,000. The blood cholesterol was 416 mg. per 100 cc. The basal metabolic rate was -33 per cent. The electrocardiogram showed normal QRS complexes and flat T-waves in all three leads. Roentgenogram of the heart showed the transverse diameter to be 12.1 cm. and the thorax 25.5 cm. Roentgenogram of the skull showed no enlargement of the sella turcica.

The patient was given only 1 grain of thyroid daily because of anginal symptoms. On July 9, thirty-two days later, her weight was 134 pounds, blood cholesterol was 210 mg. per 100 cc. She was much improved. Two months later she weighed 125 pounds and the pulse was 90. The dose of thyroid was increased to 12 grains a week. On November 30, 1943, the weight was 124 pounds, pulse 74.

The patient was perfectly normal in every way at this time. She had no more shortness of breath or substernal distress. The periods had become normal. There was less pigmentation, the hair on the neck and chest disappeared, the hair on the face was about three fourths gone, and there was less hair on the arms.

Since it was not thought in the beginning that the hair growth was related to myxedema, urinary hormonal studies were not undertaken until one month after treatment was instituted. The total androgens were as follows: July 9, 1943, 4.5 mg.; five months after treatment, November, 1943, 8.5 mg. Three weeks after stopping thyroid, December 11, 1944, two twenty-four-hour urine specimens, one on restricted fluids and one on unlimited fluids showed the following results: 6.5 mg., volume 800 cc., and 9.3 mg. and volume 1945 cc. On June 9, 1943, a weakly positive test for follicle-stimulating hormone was demonstrated, which indicates a slight excess over normal.

**Comment**—The excessive hair growth in this case strongly suggests increased adrenocortical activity and its disappearance during thyroid administration indicates cessation of that overactivity. That the pituitary gland can be overactive in at least some of its hormonal constituents in myxedematous patients has been demonstrated in the finding of excess thyrotropic hormone and gonadotropic hormone in the urine. Hypertrichosis may also occur almost any time in the female but particularly at those times when

gonadotropic activity is the greatest, *viz.*, puberty, pregnancy, and the menopause.

All writers are agreed that the thyroid-stimulating hormone is increased in postoperative myxedema; in fact, it has often been demonstrated following subtotal thyroidectomy even when no myxedema exists. It has been found in most of the cases of spontaneous myxedema. Some have suggested that myxedema may be of pituitary origin where thyroid-stimulating hormone is not demonstrated. In rare cases of pituitary tumor a clinical picture of classical myxedema is found; this is in contrast to most individuals with hypopituitarism who, in spite of a low basal metabolic rate, have a smooth, soft skin, normal blood cholesterol, and are not usually mentally retarded. Evidence is accumulating that only one pituitary hormone may be lacking without tumor, so that it is a distinct possibility that primary myxedema due to thyrotropic hormone deficiency may exist. In so far as we have been able to determine from the literature, no patient with classical myxedema has responded to thyrotropic hormone. Many patients with low metabolic rates responded to thyrotropic hormone, but so do normal individuals. In other words, as long as there is any functioning thyroid tissue, the thyrotropic hormone will be effective.

The similarity of the gonadotropic response of the pituitary to castration and the production of thyrotropic hormone following thyroid removal is to be noted. That other secretions of the pituitary may be stimulated in either case is a distinct possibility and, in fact, there is considerable evidence to justify such a conclusion. Suspicion can be diverted, especially to the adrenotropic hormone or hormones of the pituitary. Urinary 17-ketosteroids are derived at least in part from the adrenals and probably entirely so in females and male castrates.

Compensatory maintenance of 17-ketosteroids after castration in males would suggest that there has been a simultaneous stimulation of the adrenals alone with the increase of pituitary gonadotropic hormones. Hamblen *et al.* demonstrated increased 17-ketosteroids in intercurrent amenorrhea, in the menopausal period, and a final tapering off long after the menopause began. This he attributes to adrenocortical activity. Naturally, in these cases there was also increased gonadotropic activity, suggesting a costimulation of the gonadotropic and adrenotropic hormones. There is some evidence to suggest the inclusion of the thyrotropic hormone in this collaboration. Gonadotropic activity may exist and be in excess in cases of myxedema so that the myxedematous state itself does not necessarily prevent the elaboration of pituitary hormones.

Many have noted pituitary hyperplasia in thyroid deficient states. Changes in the pituitary have been demonstrated following thyroidectomy in animals. Severinghaus reported an increase in basophilic cells. This is possible corroborative evidence of pituitary costimulation since basophilic cells are thought to be associated with gonadotropic and adrenotropic activity.

Smith demonstrated pituitary and adrenal enlargement on injecting lactone, a degradation product of estrone, into intact animals. Estrone alone caused no change. This action was brought about through the pituitary, since hypophysectomized animals showed no response. If the male animal was castrated, both lactone and estrone produced similar results. If progesterone was injected simultaneously with estrone in the male castrate animal, no response was elicited, showing that both progesterone and the testicular androgen (intact animal) prevented the degradation of estrone into

lactone or a similar product. Thus, it is possible that in view of the usual amenorrhea of myxedema, and the faulty liver metabolism, as well as bodily metabolism, the conversion of the estrogens is retarded, along with reduced progesterone production, thus initiating estrone degradation into lactone or a similar nonestrogenic but pituitary stimulating product which in turn could produce adrenocortical hyperplasia.

Our analysis one month after treatment with 1 grain of thyroid daily revealed that the ketosteroids were on the low side. In general, ketosteroids are very low or absent in myxedema, but this may be a matter of elimination rather than actual deficiency. Water is retained in cases of myxedema as are also other urinary ingredients, creatinine, calcium, and iodine. Hollander *et al.* have shown that 17-ketosteroids do vary with urinary output. It would have been of interest to determine the urinary androgens during the diuresis that follows thyroid therapy in these cases. A positive follicle stimulating test was also found at this time, but again its significance here is of very doubtful value, except to demonstrate pituitary activity.

If the preceding remarks offer a possible explanation of excessive hair growth in this case, what happens then in the usual case of myxedema wherein hair loss or retardation of hair growth is frequent? To correlate the two disease phenomena, the reactivity of the end organ, namely, the skin and hair, must be considered. The various degrees of change in skin and hair in well marked cases of myxedema indicate variable reactions to the same disorder; therefore, it is not impossible that in this case there was little, if any, interference with end organ reaction. A more satisfactory hypothesis would be welcomed.

**Summary**—A case of myxedema is reported in which excess hair growth occurred and then disappeared after thyroid therapy. The possible but obviously inadequate theoretical explanations are presented.<sup>11</sup>

### Hirsutism in Females; a Clinical Study of Its Etiology, Course and Treatment

Many instances of virilized women may be found in the literature, most of whom have been suffering from adrenal, pituitary, or ovarian tumors. The earliest of these reports are little more than clinical observations, some with appended pathological findings.

The actual occurrence of functional endocrine tumors is fairly rare. In contrast, the occurrence of hirsute women is common. In the past two years, they have seen more than 200 such patients. Their complaints were mainly cosmetic; however, the altered emotional state became a most striking feature.

A few pertinent experiments on animals demonstrate the following facts: Well-fed adrenalectomized rats demonstrate precocious hair growth. Underfed normal rats have delayed growth of hair even when skeletal growth continues. In these underfed animals, the adrenals hypertrophy, and removal of these enlarged glands causes growth of new hair within forty hours after adrenalectomy. Administration of estrogens retards hair growth in rats, guinea pigs, and dogs. Concomitant administration of androgens prevents this effect in rats. Gonadectomy in fowls often causes changes in plumage, which in birds is somewhat analogous to hair. Pituitarectomy and thyroidectomy have been shown to exert influence upon the piliary system of various animals.

Important as is this work in demonstrating some degree of hormonal con-

trol on mammalian hair growth, most of it is not applicable to man, whose piliary system is unique in several ways. The most obvious sign of this dissimilarity is the marked difference in hair development on contiguous body areas in man. Thus any discussion of human hair growth should include consideration of (1) hair growth *per se*, and (2) possible secondary influences. Much of the work on the first subject has been performed, and recently reviewed by Danforth. He states that although humeral control of human hair growth probably exists, the final product of each individual follicle is largely determined by constitutional factors within the hair cell itself. Thus, considering the humeral complexes of the male as one factor, and of the female as another, there are some follicles unaffected by the difference, while in others the effect may range from slight to profound. In other words, there is a constitutional gradient of response of each individual follicle to the hormonal influences which are presumed to be equally accessible to all. This might explain why two morphologically identical follicles may produce fine body hair until puberty, when the product of one changes to long terminal hair, while the product of the other continues unchanged throughout life.

On the basis of this concept, Danforth offers the following classification of hair. First, general body hair ("lanugo" or "vellus"), which is uninfluenced by endocrine factors. Secondly, ambosexual hair, present in males and females, but dependent on hormonal stimulation which is apparently equivalent in both sexes. The axillary and pubic hair exemplify this type. Thirdly, truly sexual hair, represented by the beard of the male, and less clearly by the terminal hair of the shoulders, anterior chest and abdomen. The head hair, or capitus, is probably a

secondary sexual characteristic also, since its weight per unit of length is greater in males.

The adrenal cortex, gonads, thyroid, and anterior pituitary are the endocrine glands mainly concerned with hair production. The influence of the adrenal cortex on female ambosexual hair growth has recently been emphasized. In panhypopituitarism and in Addison's disease, conditions in which the adrenal cortex is virtually nonfunctioning, axillary and pubic hair is absent. The adrenal cortex in hypo-ovarian dwarfs, although present, is of subnormal size; likewise, the axillary and pubic hair is present but diminished in amount. The ovaries and anterior pituitary apparently exert no direct influence on ambisexual hair growth in the female. The maintenance of ambisexual hair after the menopause is also an indication of the absence of ovarian influence.

In the male, there may be more complicated factors influencing the growth of ambosexual hair. Males with panhypopituitarism, and thus secondary adrenal cortical and gonadal hypofunction, have little or no axillary or pubic hair. Men with Addison's disease have sparse pubic and axillary hair, although it may not be abundant. Testosterone has been found to increase the size and number of the pubic sebaceous glands in prepubertal boys. It would appear that male ambosexual hair growth is apparently conditioned by a synergism between the gonads and adrenals.

The beard of the male would seem to be influenced chiefly by testicular secretions. Supporting this assumption is the absence of the beard in prepubertal castrates and its disappearance following postpubertal castration. Hypopituitary males, who have secondary hypogonadism, likewise have no beard. Men suf-

fering from Addison's disease do not experience such loss.

The ambosexual hair in both sexes, and the beard in males, are diminished or absent in myxedema.

Although the general body hair is supposedly uninfluenced by endocrine factors, clinical observation would seem to indicate that this is not entirely true. One of the characteristic features of patients suffering from panhypopituitarism is the virtual absence of body hair. These effects may, of course, be mere reflections of a generally altered metabolism.

There are two major influences on hair growth, one constitutional, the other humoral. The constitutional factor is the capability of response of each individual follicle to endocrine stimuli. The humoral factor represents the various hormones supplying the stimulus for hair production to those follicles inherently sensitive to their action. Other local factors such as follicular nutrition, nerve, and blood supply must also exert their effect.

Since the control of normal hair growth is still obscure, any discussion of the causes of pathological hair growth is difficult. Hirsutism is defined as excessive hair growth, but there is no clear-cut distinction as to what type of hair is involved. Also, there is a tremendous variation in the quantity and distribution of body hair in normal subjects. Redlich has classified hair distribution in the male, but he included only body hair patterns, which are presumably less affected by endocrine factors.

Schwartz quotes some of the continental literature reporting hirsutism associated with teratoma, neurites, mumps, and encephalitis.

**Clinical Material** - Thirty-three patients have been observed during a period of three years. The patients ranged



from nineteen to sixty-seven years of age. Twenty-two of the group were married and the majority were hirsute before their marriage.

Since hirsutism occurs either in the presence of some pathologic lesion, or as an abnormal response during some physiological state, we employed the following classification in cataloging our patients.

- I. Permanent Hirsutism--
  - A. Pituitary
  - B. Adrenal cortex
  - C. Gonads
  - D. Hypothalamus
  - E. Other lesions (pinealoma, thymoma, etc.)
  - F. Idiopathic:
    1. Postpubertal
    2. Postpregnancy
    3. Postmenopausal
    4. Genetic
      - a. Familial
      - b. Racial
    5. Unclassified
- II. Transient Hirsutism--
  - Pregnancy
  - Therapeutic
  - Other causes (burns, etc.)

In our series of thirty-three patients, twenty-nine fall into "the idiopathic" class. Of these, twenty are of the postmenarcheal type, four postpregnancy, two postmenopausal, two familial, and one unclassified. Four additional patients (one pseudohermaphrodite, one acromegalic, and two cases of transient hirsutism) are discussed separately.

One patient had auburn head, pubic, and axillary hair. Soon after puberty, she developed an extension of her pubic hair over her abdomen. Two distinct abdominal triangles with opposing bases resulted, one of auburn hair, representing the original normal female distribution, and the other of black hair, indicating the more recently acquired male escutcheon.

Two of our patients, each Italian, were excellent examples of familial hirsutism. One had three hairy sisters, a hirsute mother and grandmother. She had heavy facial hair, male pubic hair distribution, and marked increase in hair over her extremities and shoulders. The other patient had five daughters and several granddaughters who showed marked generalized hirsutism. Even the five-year-old granddaughter of this patient had a well defined mustache and beginning facial hirsutism. None, however, displayed male pubic hair.

Two patients were representatives of the postmenopausal type. Both had typical sparse, long, curly chin hair and well marked mustaches. Otherwise, their body hair was normal.

Two patients (M. J. and M. M.) displayed mustaches only, unassociated with abnormal body hair.

Aberration in sexual structure and function is an integral part of hyperadrenocorticism. It is classically associated with weakness, genital and breast atrophy, and sexual underfunction. The adrenogenital syndrome involves an overproduction of androgenic, anabolic factors, and is associated with increased strength, good musculature, and genital hypertrophy.

The effects of androgenic overproduction depend upon the time of its occurrence. If the process begins *in utero*, pseudohermaphroditism results; if it is delayed until sexual maturity is attained, the adrenogenital syndrome ensues. An enlarged clitoris is one of the classic signs of this latter disease.

The clitoris was definitely enlarged in eleven of these patients. In each there was also a male configuration of pubic hair. They were among the most bearded of the group.

In fifteen patients, the labia majora were hypertrophied, two had infantilism

of the internal pelvic structures. Another was found to have atrophic ovaries at operation. The rest had apparently normal internal pelvic organs.

In these twenty-nine patients, menstruation was normal in sixteen, and irregular in twelve, often with six-month intervals between periods. One patient had never menstruated. Four of the eleven patients with clitoral enlargement had perfectly normal periods. Libido was low or absent in twelve patients, apparently normal in the remainder.

The breasts were well developed in twenty-seven patients; in fact, there was a tendency toward increased development.

Obesity is a counterpart of adrenal cortical hyperfunction, especially the Cushing syndrome. Recently, however, it has been emphasized that this obesity is not extreme and may be merely a redistribution of fat, which may give a superficial appearance of obesity. The actual weight of children with adrenocortical "obesity" is not greatly increased over the average. That adrenal cortical "obesity" is actually fat and not merely tissue fluid was recently reported.

By comparing the actual weight with the ideal weight of each patient for her height and age, it was found that there was an actual increase in weight present.

The fat in our patients was largely confined to the trunk. The arms and legs were inclined to be normal or even slender. Most of the group had broad faces, thick necks, and heavy shoulders. Usually, the abdominal fat panniculus was increased, and the hips broad and fat. In none was the fat painful to pressure. The obesity did not seem refractory to weight reduction.

It is often assumed that acne is related to excessive androgen formation and acneiform lesions are frequently described with Cushing's syndrome.

Marked acne was observed in five of this group, slight acne in two others.

Reddish-purple striae on the abdomen and shoulders were noted in seven patients. Eight of the group complained of the appearance of ecchymoses upon relatively slight trauma.

Benign hypertension was found in six patients, all of whom were over forty-two years of age.

Mild diabetes is one of the features of certain types of increased adrenal cortical function. The diabetes of hyperadrenalcorticism is insulin resistant.

Five of our patients had classical diabetes mellitus. All were insulin insensitive as measured by the foregoing test. Fourteen of the remaining twenty four showed abnormal glucose insulin tolerance curves. All of the patients except one were obese.

In the female, it is believed that all of the 17-ketosteroids are produced by the adrenal cortex.

In this laboratory, the normal range of excretion of total ketosteroids in adult females is from 5 to 10 mg. per 24 hours. Collections were always made when the patients were in excellent health and free of the most trivial infections, since even mild infectious states are known to lower steroid output. It will be noted that the great majority of these patients had 24 hour 17 ketosteroid excretions within the normal range, or in a range considered definitely subnormal for adult women. This latter finding has surprised us considerably, and we are unable to explain it. Some what high values were found in four patients, all of whom showed severe virilizations. Three patients also exhibited slightly elevated values. The first two of these exhibited hypertrophy of the clitoris.

**Radiographic Studies** Roentgenograms of the skull, sella, spine, pelvis,

and long bones were obtained in each case. In each, the sella turcica was normal. No abnormalities were detected in the long bones, or epiphyses. Two patients showed slight osteoporosis of the spine. One of these probably had postmenopausal osteoporosis, while the other patient had Cushing's syndrome.

All patients had flat films of the abdomen for kidney outline and position. If any displacement was noted, intravenous or retrograde pyelography was then employed. We did not feel that perirenal air injections for roentgenographic studies were justified in most of these cases.

Qualitative test of the urine (Sulkowitch test) showed no evidence of hypercalcinuria save in one case. Red blood cell counts and hemoglobin determinations gave no evidence of polycythemia. In seven of the more severe cases, estimations of sodium, potassium, chloride, and  $\text{CO}_2$  were performed, but no deviation from the normal was observed.

Estimations of gonadotropins were made in several cases. It is interesting that in two instances, although the patients were still menstruating, assays of the urine for the follicle-stimulating hormone showed that more than 10 rat units were excreted per 24 hours, indicating hyperfunction of the pituitary gland.

### CASE REPORTS

**Case 1**—A nineteen-year-old student nurse was admitted to the hospital May 27, 1941, because of a typical attack of renal colic on the left. At the age of twelve she began to have painless menstrual periods of eight days' duration occurring at intervals of two to four months. For five months before this hospitalization, she had had no menses. At seventeen, she noticed an abnormally large amount of hair on her face, abdomen, arms, and legs. Soon it became necessary for her to shave daily. She had a large head and neck, broad shoulders, and narrow hips. The excess adipose tissue in the head and neck stood out in great contrast to very small amounts elsewhere. The breasts were relatively

small. Many muscle patterns in the extremities were readily noticeable. She weighed 137 pounds and was 68 inches tall. There were patches of brown pigment over the chin, neck, axillae, areolae, breasts, and abdomen. A heavy beard was present and there was a moderate increase of coarse black hair over shoulders, extremities, and abdomen. A male escutcheon was noted. There were no striae. Acne was not present. The blood pressure was normal. The labia majora were distinctly large and pouty and the clitoris was twice normal size. The uterus and ovaries seemed to be normal.

Red, white, and differential blood cell counts were normal. The Sulkowitch test for calcium gave a strong reaction, even after the patient's diet had contained only a small amount of calcium for three days. Blood chemical studies showed the sodium to be 141 m. eq. per liter, potassium 4.5 m. eq. per liter, nonprotein nitrogen 34 mg. per 100 cc., calcium 10.2 mg. per 100 cc., phosphorus 3.8 mg. per 100 cc., phosphatase 3.4 Bodansky units, cholesterol 154 mg. per 100 cc., and total protein 7.1 gm. per 100 cc. Roentgenograms of the sella turcica, chest, hands, humeri, femora, and pelvis were normal. The development of the bones was in accordance with the age of the patient. Pyelograms showed two small calculi in the left renal pelvis, and a small one in the right renal pelvis, but no displacement of either kidney.

An assay of a twenty-four-hour specimen of urine for 10 rats units of follicle-stimulating hormone was negative. The excretion of 17-ketosteroids was found to be 7.4 and 10.3 mg. during two periods of twenty-four hours. In the latter specimen, 10.1 mg. of the alpha fraction were present. Stained smears of vaginal scrapings taken at intervals showed an estrin effect but never a luteal effect.

On July 21, a left pyelolithotomy was performed. The left adrenal was found to be somewhat enlarged and about one half of it was removed. Cut section showed the center to be thicker than normal and fat stains revealed an excessive quantity of lipoid. Within a week after operation, the patient had her first menstrual period in six months. The flow lasted for seven days and was associated with cramps, suggesting that a secretory endometrium was present. An endometrial biopsy obtained one day before the next period, one month later, demonstrated a secretory endometrium. Following operation no change in the hair growth was noted, but there was a slight increase in breast development. There were 13.4 mg. of 17-ketos-

teroids, 10.0 in the alpha fraction, excreted on August 22, and the total excretion on August 30 was 6.8 mg. The serum sodium and potassium remained normal.

By this time we had some evidence that the patient was suffering from hyperadrenocorticism which presumably had resulted from the excessive production of adrenotropic hormone. Experience has illustrated that in patients with disorders of the type encountered here, neither roentgenotherapy nor surgery directed toward the adrenals or pituitary has been of much aid. Thereupon, we attempted to produce an "anti-hormone effect" by the prolonged administration of adrenotropic hormone. On September 3, she began receiving subcutaneous injections of adrenotropic hormone, 1 cc. daily. Five days later, the dosage was increased to 1 cc. twice daily, and this was continued until October 9. During the course of treatment the only clinical change observed was that the patient developed an increased desire for salt and complained of slight sensitivity to cold. On September 14, the excretion of 17-ketosteroids was 7.0 mg., 6.6 mg. of which was in the alpha fraction; October 5, the excretion was 13.3 mg. with 11.2 mg. in the alpha fraction. No change occurred in the serum sodium or potassium.

For two months after the adrenotropin therapy, no treatment was given. During this time the patient's clinical status remained unchanged. On October 28, a glucose insulin tolerance test, using 65 gm. of glucose, orally, and 6.5 units of insulin, intravenously, yielded evidence of insulin resistance as indicated by the following changes in blood sugar, expressed as milligrams per 100 cc. of blood: 84, 105, 137, 151, 171, and 154, the specimens having been obtained at 0, 20, 30, 45, 60, and 120 minutes after the test was begun. Urine specimens saved over a period of four days (December 13 to 17) contained an average of 12.5 mg. of 17-ketosteroids per day. Thus it would seem that the adrenotropin therapy had afforded no definite benefit.

We next considered the possible effects of the administration of ovarian hormones in large doses. We treated our patient with a large amount of progesterone, 25 mg. intramuscularly daily, for two months, during the last month of which 1.66 mg. of alpha estradiol benzoate was given intramuscularly three times weekly.

During treatment, a definite enlargement of the breasts and hips resulted, but there was no change in the hirsutism. The progesterone therapy given alone or in conjunction with alpha estradiol benzoate had no definite effect on the

nitrogen, sodium, potassium, or calcium balances. The excretion of 17-ketosteroids was less (average of 5.1 mg. daily for four days) at the completion of therapy than had been found at any other time. However, a determination of the 17-ketosteroids one month later showed a return to the previous high level.

The patient developed an attack of renal colic on the right, and passed a small stone in the urine. A roentgenogram of the abdomen showed several small stones in the right kidney. On March 29, 1942, the right adrenal and kidney were explored surgically. The adrenal tissue otherwise appeared normal. A tuberculous sinus developed at the operative site and required several months to heal.

On July 17, 1942, the 17 ketosteroid excretion was 16.3 mg. It is to be emphasized that this was one of the highest values obtained in this case and was determined after the patient had been in bed several months with a chronic infection--factors which tend to lower the 17-ketosteroid excretion. On December 6 and December 30 she excreted 1.9 and 4.3 mg. of 17 ketosteroids, respectively.

**Case 2**--L. T., physical examination revealed an obese, hirsute woman with vague abdominal tenderness. Laboratory examinations were within normal limits. The 17 ketosteroid estimation was 12 mg. per twenty four hours. Intravenous pyelograms showed partial fixation of the left kidney; perirenal insufflations were not conclusive but it was thought that there was enlargement of the left adrenal. She was discharged without further study.

She was admitted to the medical wards of the Massachusetts Memorial Hospital on March 18, 1943, complaining of a progression of her hirsutism. She stated that she had gained 20 pounds in weight in the past three years, and had noted a definite increase in strength. Her voice had grown deep and had "cracked" several times while singing. Her skin had become increasingly greasy, acne had been present for eight or nine months, and some purplish-red striae had appeared over her arms and shoulders. Her face had become broad. Her catamenia had begun in her teens and had been regular until about one year previously. During the year preceding this hospitalization, her periods were often seven to eight weeks apart and lasted for intervals varying from three to seven days.

The skin was moist and pink; striae were present over the deltoid region and abdomen; acne was marked, especially on the face. The

hair was increased greatly on the face, forearms, legs, and around the nipples. The pubic hair followed a male pattern. The visual fields were normal. The thyroid gland was normal in size. The heart and lungs were normal. There was slight tenderness of the right kidney, where it was thought there was a palpable mass. Pelvic examination revealed normal labiae, a normal clitoris, and a retroverted uterus.

The red, white, and differential blood cell counts and urinalyses were normal. The spine showed some scoliosis in the dorsal region with slight decalcification. A twenty-four-hour specimen of urine gave a negative assay for 10 rat units of follicle-stimulating hormone. There were 12 mg. of 17-ketosteroids excreted in the urine in twenty-four hours. The perimetric fields were normal.

Because of the sudden progressive nature of her symptoms and the questionable enlargement of the left adrenal suggested by perirenal insufflation, the patient underwent an exploratory laparotomy on April 14, 1943. At operation, an abnormal mass was thought to exist at the upper pole of the left kidney. The right adrenal was not enlarged. Both ovaries were small and atrophic. The uterus was slightly enlarged and contained fibroids. On June 6, 1943, a left adrenalectomy was performed. Although at operation the left adrenal gland was thought to be somewhat enlarged, the pathological report was "histologically normal adrenal."

She was discharged on June 19, 1943. Soon after her operation, the patient stated that she felt weaker, and also that her beard required less attention. She lost 30 pounds and her periods were reestablished at monthly intervals. Despite her statements, we have observed no effect on her hirsutism.

**Case 3**—A forty-two-year-old white female was admitted to the Thorndike Ward on August 20, 1943, complaining of uncontrolled diabetes for some years, increased facial hair, and pain in the back.

Menarche occurred at eleven years and menstruation was often grossly irregular. She successfully underwent seven pregnancies, the last at the age of thirty-two years. Ten years previous to admission (almost immediately after her last delivery) she noted the onset of polyuria and polydipsia. At this time glycosuria was discovered. She continued to lactate for several years and noted the growth of a heavy black beard, which progressed to date and which required daily shaving. The hair of her head had thinned. The patient had been obese for

about fifteen years, her greatest weight being 225 pounds.

About nine years before admission, she was operated upon for an ovarian cyst. She recovered successfully and was discharged on a diet of 70 units of insulin daily, which did not adequately control her diabetes. Her diabetic state remained uncontrolled despite numerous attempts to improve it.

In March, 1941, she was admitted to the Massachusetts General Hospital, where it was found that she had diabetes of the insulin-resistant type, as evaluated by insulin and glucose-insulin tolerance tests.

The patient was given a ketogenic diet, without insulin (although she had been taking 70 units previous to admission). She did not develop ketosis and noted no subjective change except increased weakness. When she was given a normal diet, she felt better but there were no appreciable changes in her blood or urinary finding.

In June, 1941, she was admitted to the Massachusetts Memorial Hospital complaining of headaches. Her blood pressure was 142 mm. Hg systolic and 100 mm. Hg diastolic. A lumbar puncture, performed to relieve the headaches, showed an initial pressure of 220 mm. of water (although the patient possibly was not relaxed). An intravenous pyelogram was interpreted as showing an enlarged left kidney. The 17-ketosteroid excretion was 18 and 14.4 mg. per twenty-four hours respectively, on two occasions. A later course of roentgen-ray therapy directed to the pituitary had little apparent effect on her diabetes.

Physical examination revealed a middle-aged woman with plethoric features and marked girdle obesity. The blood pressure was 140 mm. Hg systolic and 90 mm. Hg diastolic. Black hair was present in increased amounts on the upper lip, chin, arms, legs, and abdomen, the latter having a male pattern. The skin was thin, reddish-purple striae were present over the shoulders and hips, and the superficial veins were prominent. There were one or two (spontaneous) bruises on her lower extremities. The thyroid was palpable and there was a firm nodule to the right of the isthmus. The lungs and heart were normal. The abdomen presented a large panniculus of fat; no internal organs or masses were palpable. Pelvic examination revealed hypertrophy of the major and minor labiae, and a clitoris about twice the normal size.

Blood cell counts were normal. Repeated urinalyses showed a 4 plus sugar reaction.

Fasting blood sugars varied from 180 to 252 mg. per 100 cc. There were 95 m. eq. of chloride per liter of serum; total protein, 6.9 gm. per 100 cc. of serum. The glucose and insulin tolerance test gave the following values: 204, 222, 270, 292, and 345 mg. of sugar per 100 cc. of blood, the samples having been taken at 0, 30, 60, 90, and 120 minutes respectively. Two determinations of the basal metabolic rate were within the normal range. Roentgen rays of the sella turcica and intravenous pyelograms were normal.

On September 8, 1942, she was discharged on her previous diet of carbohydrate 150, protein 70, fat 60, and was told to take 24 units of protamine insulin daily before breakfast. She has been taking thiouracil, 0.2 gm., daily for eight months, but has noted no change in her hirsutism.

**Discussion**—These three patients present certain of the manifestations of Cushing's and of the adrenogenital syndrome. Recently, another such patient has been reported, again emphasizing the inadequacy of our diagnostic aids. Together, these three cases also provide all the comment necessary on the ineffectuality of surgery, roentgen, and medical therapy on the progress of the hirsutism.

### Hirsutism Associated with Acromegaly

Hirsutism is sometimes associated with acromegaly. One such case was observed in our group.

**Case 4**—A fifty-year-old white unmarried female was admitted on July 11, 1941, in marked cardiac failure. Twenty years previous to her admission her features grew coarse, her hands enlarged, her voice deepened, and headaches began to accompany her menses. Seventeen years before admission she underwent a leiomyectomy, followed by amenorrhea, which persisted until two years previous to admission, when she had several normal catameniae. Amenorrhea then recurred. Sixteen years prior to the present entry, she developed diabetes mellitus and thyrotoxicosis. An adenomatous colloid goiter was removed. Six years later, hirsutism developed. During the four years preceding admission, fasting blood sugars ranged from 178 to 322 mg. per 100 cc., and blood pressures

from 210 mm. Hg systolic and 110 mm. Hg diastolic to 140 mm. Hg systolic and 80 mm. Hg diastolic.

Physical examination revealed an orthopneic, well nourished, middle-aged woman with acromegalic features. The upper lip and jaw were very hairy. The skin was thick and coarse. The hands and feet were large. The temperature was 98° F.; pulse, 100; respiratory rate, 30 per minute, and blood pressure, 148 mm. Hg systolic and 112 mm. Hg diastolic. A thyroidectomy scar was present, and an increased amount of adenomatous thyroid tissue was palpated. The lungs revealed dulness and moist râles at the left base posteriorly. The heart was enlarged, and there was a systolic murmur at the apex. The liver was enlarged and tender. The pubic hair had a male pattern, but there was no hypertrophy of the clitoris. There was extensive pitting edema of the ankles, legs, and sacrum. The neurological examination was normal.

Laboratory tests revealed the following: Blood cell counts were normal. Numerous urines showed 1 plus to 4 plus albumin, and no sugar. The nonprotein nitrogen was 25 mg. per 100 cc.; chlorides, 100 m. eq. per liter; cholestrol, 250 mg. per 100 cc.; calcium, 10 me. per 100 cc. of serum; phosphorus, 3.9 mg. per 100 cc. of serum; phosphatase, 4.5 Bodansky units; total protein, 5 gm. per 100 cc. Numerous fasting blood sugars were less than 120 mg. per 100 cc., with one exception, which was 175 mg. per 100 cc. The roentgen ray of the skull was interpreted as showing Paget's disease; roentgen rays of the hands showed elongation of the first metacarpals. The basal metabolism was minus 12 per cent (after partial recovery from cardiac failure). The follicle-stimulating hormone assay was positive for 18 rat units. The 17-ketosteroid excretion was 4 mg. per twenty-four hours. A glucose insulin tolerance test showed values of 107, 144, 179, 175, 222 mg. per 100 cc., specimens having been taken at 0, 30, 60-, 90-, and 120-minute intervals.

**Postmortem Examination** The external appearance was that already noted in the antemortem examination. The liver was slightly enlarged (2480 gm.), extending 4 cm. below the costal margin. The spleen (320 gm.) showed a small area of infarction. The pleural cavity had many adhesions on the right, with a small quantity of serous fluid in the right base. The heart (620 gm.) showed hypertrophy of both ventricles and considerable dilatation of the right auricle. Both coronary arteries were atheromatous. An adherent, pale-gray thrombus

was present over both surfaces of the anterior half of the interventricular septum.

The examination of the endocrine organs was as follows:

**Pituitary**—The organ weighed 1 gm. The anterior lobe contained a soft necrotic area, which comprised one third of its bulk. Histologically, it was found that much of the anterior lobe consisted of a pituitary eosinophilic adenoma largely destroyed by a recent infarct. The cells of the remaining portion of the gland showed a predominance of basophiles.

**Thyroid**—The lateral lobes were of usual size, and contained numerous cysts and much fibrous tissue. Microscopically there was great variation in the size of the follicles, most of which were filled with old colloid. There was no epithelial hyperplasia.

**Adrenals**—The right adrenal weighed 16 gm., the left 12 gm. They were firm, and there was a very deep yellow color of the cortex. Histologically, there was no hyperplasia of the cortices.

**Genital Organs**—The uterus was small and firm, displaying an inactive endometrium. The ovaries were small (5 cm. in diameter). No follicles were seen.

The pancreas and parathyroids were not grossly or histologically remarkable.

**Discussion**—This patient's clinical history suggests that twenty-five years previous to our observation, she began to develop her pituitary tumor. The headaches at this time were probably due to enlargement of the neoplasm. In response to increased growth hormone production, her features grew coarse, and her hands and feet enlarged. A few years later, presumably as a response to increased thyrotropic and pancreatropic stimulation, she developed hyperthyroidism and diabetes mellitus. As evidence of probable adrenal stimulation are the hirsutism and amenorrhea. About two years before her final admission, some reverse of a previously progressive process seems to have occurred. This was not brought about by the infarct found at postmortem examination, however, since the latter was of more recent occurrence. She had the onset of myxedema-

tous symptoms, concurrent improvement of her diabetes, and occasional menses. Despite improvement in most of her findings, the hirsutism did not disappear. It is also interesting that the case shows marked secondary adrenal hypertrophy which probably explains the persistence of facial hair. A similar case of acromegaly reported by Kennedy (quoted by Schwartz) underwent a posthypophysectomy remission of all symptoms save the hirsutism. The low 17-ketosteroid excretion in this patient was probably due to poor clinical status.

One patient had hyperplasia of the gums similar to the "partial acromegaly" described by Zondek. This may be merely a congenital characteristic, however, since it has occurred in other members of her family.

#### **Hirsutism Associated with Adrenal Disease—Pseudohermaphroditism—**

According to the most accepted concepts, the pseudohermaphrodite represents virilization due to adrenal hyperfunction. We have observed one such case which exhibited "hirsutism" as a precocious appearance of abundant axillary and pubic hair.

**Case 5**—An eight-year-old white girl was admitted to the Massachusetts Memorial Hospital September 21, 1943. Her birth history was normal. At the age of one year, a doctor had noted unusual clitoral enlargement and had advised investigation. The family noted progressive enlargement of the organ but deferred treatment. The patient had always exhibited thoroughly feminine habits and was unaware of her abnormality. The family history was irrelevant.

The physical examination revealed a shy, feminine-acting girl, with a very deep masculine voice. She was slender and her body habitus was masculine. She was the size of a twelve-year-old girl, weighing 91 pounds and measuring 57 inches in height. Her strength was distinctly better than normal. The blood pressure was 150 mm. Hg systolic and 70 mm. Hg diastolic. She had considerable facial acne. The skin was seborrheic. The pubic and axillary hair was well developed. The thyroid was not enlarged.

The heart and lungs were normal. No abdominal masses could be palpated. Pelvic examination revealed well developed labiae majorae covered with abundant hair. The clitoris was a large, penislike structure, three inches in length, with a well-developed glans. On the inferior surface, a frenulum was present, running back into the vestibule. On the inferior aspect of the frenulum was several openings, one of which proved to be the urinary meatus. Cystoscopic examination revealed a normal bladder. The vagina was well developed.

Laboratory studies revealed the following: Red, white, and differential blood cell counts and urinalyses were normal. The basal metabolic rate was plus 2 per cent. The fasting blood sugar was 94 mg. per 100 cc.; total protein, 7.0 gm. per 100 cc. of the plasma; calcium, 10.9 mg. per 100 cc. of serum; phosphorus, 3.8 mg. per 100 cc. of serum; alkaline phosphatase, 11.4 Bodansky units; sodium, 336 mg. per 100 cc. of serum. The glucose tolerance test gave the following values: 125, 89, 100, and 60 mg. per 100 cc., the samples having been taken at 0, 30, 60, and 120 minutes. The insulin tolerance test gave values of 111, 80, 85, and 90 mg. per 100 cc., the samples having been taken as above. Intravenous pyelograms were normal. The sella turcica was normal. Roentgen rays of the long bones and epiphyses showed development consistent with that of a fourteen-year-old girl. There were 8.4 and 14.1 mg. of 17-ketosteroids excreted per twenty-four hours in two samples assayed.

On October 8, 1943, an exploratory laparotomy was performed. The uterus, tubes, and ovaries were normal. Both adrenals were palpated, and the right was thought to be enlarged. On November 26, 1943, through a right lumbar incision, the right adrenal gland was found to be "larger than an adult's adrenal gland." A resection of one half of the gland was performed, since the size of the other gland was unknown. Histological examination of the resected adrenal revealed cortical hyperplasia.

Six months following the operation, the patient's voice was of higher pitch, although still resembling that of a boy. Acne was much improved. There was some increased areolar pigment and beginning mammary development. The genitals were unchanged. The laboratory studies were essentially unchanged. The 17-ketosteroid excretion, however, had dropped to 3.8 and 4.4 mg. per twenty-four hours, in two samples analyzed.

This patient is a classical example of pseudohermaphroditism, presumably resulting from adrenal cortical hyperplasia. Actually, it is the adrenogenital syndrome, beginning in embryonic life. The body cells are in the process of differentiation and the effects of increased androgen production are marked. The causative etiological lesion may be an adrenal tumor, adrenal hyperplasia, or a hyperfunction of some androgenic adrenal component (such as the X zone).

The effects of operation on the appearance of this girl are marked. There has been a definite diminution in androgenic influences as demonstrated by the beginning breast development, increase in vocal pitch, and lessened acne. The drop in the 17-ketosteroid excretion is a good chemical indication that there has been a diminution of the androgenic function of the adrenal. The genital malformation will undoubtedly require plastic surgery.

**Case 6**—A. C., aged twenty-eight, a white primigravida, was examined on September 19, 1941. The patient stated that her last menstrual period had occurred on July 23, 1941. In September, 1941, she first noted the appearance of rapidly growing blackish hair on her malar eminences, ear lobes, eyebrows, and upper lip. By October, 1941, her chin, mammary areolae, arms, and legs were involved. She had always had a male pubic distribution, but this had increased. The patient was not at all perturbed over her hirsutism, since her mother also had been hirsute during pregnancy, and had lost all the abnormal hair postpartum.

Past history revealed that she had always been a "big girl." At eleven years she had weighed 125 pounds. Her catamenia began at eleven years, had occurred every twenty eight days, for a five-day period.

Physical examination revealed an obese young woman with marked hirsutism. The temperature was 98.6° F., pulse 90, respiratory rate 20 per minute, weight 179 pounds and height 67 inches. The blood pressure was 125 mm. Hg. systolic and 75 mm. Hg. diastolic. Coarse black hair covered her upper lip, cheeks, chin, and jaw, and grew out of her ears and ear lobes. There was increased hair on the legs and forearms, and a pronounced male pubic hair growth was present. The areolae of the nipples were surrounded by ten or twelve long dark hairs. The thyroid was diffusely enlarged. The clitoris was slightly hypertrophied. Pelvic findings were consistent with pregnancy of three months' duration. Examination was normal.



Roentgen rays of the sella turcica were normal. The basal metabolic rate was minus 10 per cent. The 17-ketosteroid excretion was successively 15.04 and 13.92 mg. per twenty-four hours.

The hirsutism continued to increase until February, 1942. Spontaneous depilation then occurred beginning about the ears and right side of the face. Later, the hair on the abdomen and large patches on the thighs were denuded. The clitoris remained enlarged. In February, 1942, the patient had some vaginal bleeding which stopped spontaneously.

The patient went into a twenty-hour labor on May 13, 1942. She had some uterine inertia and was delivered with low forceps. The child was given early formula feedings because of oligogalactia. The hirsutism was still present at delivery but disappeared entirely postpartum.

**Comment**—It is known that the adrenal enlarges in animals during pregnancy. The hirsutism seen in human females during gestation is due presumably to similar adrenal hyperfunction. The fact that relatively few patients suffer from transient hirsutism of pregnancy suggests that other factors are also implicated. This patient had a familial history of hirsutism which suggests that genetic factors are involved. This case has several other points of interest. Although she was not hirsute previous to her pregnancy, her "bigness," obesity, and male hair distribution are reminiscent of our "idiopathic" hirsute group. Whether the clitoris was enlarged before her pregnancy or as a result of it cannot be stated. The threatened abortion, uterine inertia, and oligogalactia also seem to indicate some lowering of typical feminine function, possibly due to androgenic influences. The beginning depilation before the delivery of this patient is difficult to explain. However, it has been shown that estrogen excretion increases about the sixth month of pregnancy. It was at this time that the patient began to lose her hirsutism. With the increase in estrogens, we might postulate that the estrogenic-androgenic ratio

reached a better balance and the hirsutism diminished as a result.

Another patient with transient facial hirsutism of pregnancy whom we have seen did not lose her abnormal hair until after delivery. This individual was slender and had no family history of hirsutes. The 17-ketosteroid excretion ranged from 1.6 to 3.2 mg. per twenty-four hours on three occasions. The values are actually lower than normal.

As has been pointed out in a recent editorial, the more severe the cause of hirsutism, the more likely the cure.

There is general agreement that when the cause is a tumor, surgical removal is indicated. The results are often brilliant, with a complete reestablishment of all feminine functions and characteristics. However, even here the hirsutism may persist. Also, in the case of adrenal tumors, the opposite gland may be secondarily atrophied and unable to maintain life function. When the cause is a basophilic tumor of the pituitary, either surgical or roentgenological treatment is generally unsatisfactory. In the case of adrenal hypertrophy, resection of the cortex and unilateral adrenalectomy have caused only slight transient improvement in most cases.

Synthetic and natural estrogens have been tried, although results have not been encouraging.

Progesterone, in large doses, is reported to cause adrenal atrophy. This is apparently mediated through the inhibition of luteinizing hormone of the pituitary, which is thought to stimulate the adrenal cortex. One attempt to diminish adrenal function by this means was an apparent failure. In four patients the effect of the new antithyroid drug, *2-thiouracil*, introduced by Astwood, has been noted.

The four patients have been maintained on *thiouracil* in doses of 0.2 to

0.4 gm. daily for ten months. Two of the patients who have diabetes mellitus have discontinued insulin and have remained without sugar in the urine while on the therapy. This is probably not a direct result of drug therapy but due to the fact that they have lost some weight and have been following their diet more strictly.

One woman whose hair was quite gray now has a definite admixture of yellow. She has seen no change in the character or growth of her facial hair, although it is now removed with greater ease. After eight months of therapy (0.4 gm. daily), the drug was discontinued in this patient, due to the onset of symptoms of myxedema and depression in her basal metabolic rate.

Two other patients state that they do not shave as frequently as before the treatment, although we can note little change. The fourth woman has observed no effect of thiouracil on her diabetes or facial hirsutism. The abnormal distribution of body hair has not been affected.

**Discussion**—Although the severity of masculinization is often suggested to differentiate the "idiopathic" variety from pituitary, adrenal, and ovarian types of hirsutism, our series would not bear out this fact. Likewise, patterns of fat distribution, the quality and location of the abnormal hair produced, and the presence or absence of clitoral hypertrophy, although formerly considered to be of great significance, are of little practical use in differentiating among the various lesions.

In diagnosing adrenal lesions, the palpation of an abdominal mass is most helpful. Careful studies of the kidney adrenal area with pyelograms, and possibly perirenal air injections, may yield valuable confirmatory information. Great increases in 17-ketosteroid excretion, especially of the beta and nonalcoholic fractions, are

valuable in diagnosing cases of adrenal carcinomata. Lesser increases in 17-ketosteroid output occur in some instances of "hyperplasia."

Arrhenoblastomata of the ovary are not usually associated with hypertension, disordered carbohydrate metabolism, osteoporosis or polycythemia. It has been stated that the presence of a pelvic mass, when associated with hirsutism, an enlarged clitoris and normal excretion of 17-ketosteroids, should make one suspicious of an ovarian tumor. We have seen one patient who had severe virilization, an enlarged clitoris, low 17-ketosteroid assays, and a pelvic mass, whose ovarian "tumor" proved to be a tubo-ovarian abscess at operation. Similar findings may also occur with diffuse luteinization of the ovaries. If, after careful search, ovarian, pituitary, or adrenal causes are ruled out, the case then becomes one of "idiopathic" hirsutism.

The relationship between heterosexual hypertrichosis and certain instances of adrenal hyperfunction has been quite well established. This is most clearly acceptable with the demonstration of an adrenal lesion *per se*. In the case of pituitary tumors associated with hirsutism, adrenal hypertrophy is often demonstrable, and the mechanism seems adequately explained by an excessive stimulation of the adrenal cortex by pituitary adrenotropins. Ovarian tumors associated with masculinization presumably produce substances similar in action to the cortical steroids. There are also rare masculinizing ovarian tumors actually composed of functioning adrenal cortical cells. This is always an unsatisfactory diagnosis and especially so when we realize that most hairy women fall into this classification. At present the pathologist can give little help in the situation because of current lack of methods ade-

quate to demonstrate altered function in cells which may look anatomically normal under the usual stains.

**Summary** — Twenty-nine cases of "idiopathic" hirsutism have been studied in some detail. Twenty-four of the cases had heavy beards requiring daily shaving; twenty-three had the male type of pubic hair distribution. Clitoral enlargement was present in eleven cases. Thirteen had menstrual abnormalities. Obesity was present in the majority. Glucose-insulin tolerance tests were abnormal in nineteen cases, suggesting the possibility of an insulin-resistant type of carbohydrate defect. The 17-ketosteroid excretion was normal or subnormal in the majority of the group.

The therapy of hirsutism is generally unsatisfactory. In our series, both hormonal and operative measures were employed without success. Four cases were treated with thiouracil in doses from 0.2 to 0.4 gm. daily for eight months. The results were not encouraging.

The differential diagnosis of hirsutism is briefly discussed. It is felt that with increased knowledge of histochemical techniques, steroid chemistry and enzymology, many cases of "idiopathic" hirsutism will be found to have evidence of hyperadrenocorticism.<sup>12</sup>

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## ENDOSCOPY

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The remarkable results secured by the use of *penicillin* in acute bronchopulmonary infections have opened an extensive field in research. Studies of methods of administration have been carried out to determine the effects of local application of penicillin and it also is being employed in chronic as well as acute pulmonary infection. As is commonly the case, early reports often are unduly optimistic and only after many observers have recorded their results can we hope to secure a proper evaluation of these new agents.

**Penicillin in Bronchopulmonary Infections**—The clinical use and the

value of penicillin in the treatment of ninety-three patients with chronic infections of the lungs and bronchi were studied by Kay and Meade.<sup>1</sup> They found it to be of greatest value in the treatment of acute pulmonary infections but as chronicity developed, it becomes less effective so that in the treatment of advanced bronchiectasis it exerts no permanent benefit. It, however, does play a useful part in the treatment of pulmonary suppuration, chronic pulmonary abscess, and fungus infections in that it tends to decrease the general manifestations of toxicity, promotes symptomatic improvement, and aids greatly in pre-

paring the patient for operative intervention.

Routine bronchoscopy was done before, during, and after penicillin therapy. The course of the disease and the efficacy of the treatment were noted. Specimens of secretion were secured bronchoscopically for culture and also for determining the penicillin sensitivity of the organisms present. Although the quantity of sputum decreased and evidence of sepsis diminished, the bacterial flora was not appreciably affected.

Chronicity in pulmonary infections introduces factors which are not found during the acute stage and these seriously impair the efficiency of penicillin. These factors are mechanical, consisting of tissue destruction, fibrosis, avascularity, and bronchial occlusion.

The intratracheal administration of penicillin in the treatment of bronchiectasis and chronic bronchitis appeared to give more benefit in many cases than the intramuscular route. As much as thirty thousand to fifty thousand Oxford units of penicillin can be employed daily in one application to the tracheobronchial tree and excellent results were obtained by this method in patients with chronic bronchitis and minimal bronchiectasis.

**Administration of Penicillin by Inhalation**—Hagens and his associates<sup>2</sup> reported their results with the use of penicillin by the method of inhalation. They employed it in patients with acute and with chronic infections. A total of twenty-two were treated. Penicillin levels in the urine and blood showed that the drug is absorbed from the lungs in sufficient quantity to offer another method when penicillin therapy is indicated. Because of its local effect, it may be the method of choice in the treatment of pulmonary diseases.

Inhalations of penicillin resulted in temporary improvement in bronchiectasis, but relapses occurred frequently after therapy was discontinued. In most cases, gram negative bacteria were encountered. Asthmatic patients with a superimposed bronchial infection by an organism to which they possibly were allergic seemed to be favorably influenced by this therapy.

Acute pulmonary conditions responded satisfactorily to the inhalation treatment and it was believed that the method could be used advantageously in children and in other patients when the usual methods of administration of penicillin were unsuitable.

In a series of more than 200 patients that were treated by *Barach's aerosol penicillin* method, Vermilye<sup>3</sup> highly recommended this technic as a valuable aid for the general practitioner. He considered it as an effective and inexpensive means of treatment which eliminated some of the present difficulties of penicillin therapy. It can be readily carried out in the office or by the patient in his home. This plan of therapy and technic is of particular value in respiratory infections, since a large proportion of conditions for which penicillin is required in general practice are acute bacterial invasions and chronic infections of the upper respiratory tract.

The diseases treated successfully included acute relapsing pneumonitis due to various cocci, tonsillitis, sinusitis, and sinobronchitis, pharyngitis, and intrinsic bacterial asthma.

The technic is simple and consists of inhalation of the vaporized drug with the aid of a mouthpiece. This can be readily learned by patients and can be carried out unattended except for preliminary instructions. Children as young as two years have been given courses of inhalations successfully.

**Penicillin in Bronchiectasis**—To determine the effects of penicillin in the treatment of bronchiectasis, Stookey and his associates<sup>4</sup> gave an average dose of 1,000,000 Oxford units of penicillin to each of twenty-one patients with chronic cough over a period of eight to ten days. Administration was either by intramuscular injection in divided doses or by a continuous intravenous drip. Although the patients showed some improvement, the volume of sputum was not reduced. Studies of sputum showed that colonies of hemolytic streptococci and staphylococci were decreased.

In 20 per cent of the cases treated, most of the patients having chronic bronchitis associated with periods of activity and remission, the cough disappeared in some instances within four days. It would appear that penicillin would be of value in those cases of infection of the bronchial mucosa by pathogenic cocci that are susceptible to penicillin, but in cases where there are structural changes in the lining of the small bronchioles, little can be hoped for.

May and Hoyer<sup>5</sup> treated several patients with bronchiectasis by injections of penicillin into the trachea between the cricoid cartilage and first tracheal ring. A preliminary injection into the trachea of 2 cc. of a 2 per cent solution of *amethocaine hydrochloride* was given to allay the cough reflex and the *penicillin* was injected through the same needle. A solution of penicillin containing 10,000 units per cubic centimeter was prepared and 5 to 8 cc. injected rapidly through the needle into the trachea, the needle being withdrawn immediately and the patient urged not to cough. Posturing was employed to aid in getting the fluid into the bronchiectatic cavities. The patient was kept in this position for fifteen minutes after the injection.

Daily treatments were carried out for eight to ten days. Of three patients treated, one improved, and declined lobectomy. A second patient was enabled to get over the latter months of pregnancy, and a third patient, who was considered a poor surgical risk, was rendered fit for lobectomy. While it is inevitable that bronchiectatic cavities will become reinfected, and it is too early to give any opinion concerning the length of time that they will remain sterile, the treatment does provide at least temporary improvement in patients in whom the predominant organism is penicillin sensitive.

**Sulfonamides and Allergy Management**—In a study of bronchiectasis from the standpoint of allergy and also of treatment, Thomas and others<sup>6</sup> found that of 190 consecutive cases, approximately one half had major allergy of the respiratory tract. A study of seventy-five selected cases was carried out to evaluate sulfonamide therapy and allergy management in treatment. In fifty-five of these, an allergy of the respiratory tract was found to be an etiologic or complicating factor. Twenty-three cases received *sulfonamides* as the chief or only therapeutic measure and after observation for four months to four years, twenty-two showed definite improvement with reduction of cough and expectoration. Twenty-one cases treated chiefly or wholly with allergy management were observed from one to four and one half years. Fifteen of these showed frank improvement with reduction of cough and expectoration. Combined *allergy management* and *sulfonamide therapy* were used in thirty-one cases. They were observed for six months to five years and in twenty-six cases there was from 25 to 100 per cent improvement in cough and expectoration. They believe that in cases

of nonsurgical bronchiectasis an adequate trial of sulfonamide therapy is definitely indicated and in those with complicating allergy, management of this phase should be considered.

#### **Acute Laryngotracheobronchitis—**

Since acute laryngotracheobronchitis is not a specific entity but a clinical syndrome produced by a combination of factors, it is difficult to plan any specific therapy. The most important pathological changes encountered are mucosal and submucosal inflammatory edema involving the larynx and lower respiratory tract. The most urgent early symptoms therefore are those produced by the presence of edematous swelling of the mucosa of the subglottic larynx, namely, respiratory obstruction. It probably is primarily influenzal in origin with secondary invaders, more often streptococci, complicating the clinical picture. The only highly effective specific treatment now available is *human convalescent serum* primarily anti-influenzal and secondarily antistreptococcal. With these, the disease may be shortened and the development of complications avoided. Baum<sup>7</sup> recommended a dose of 50 to 250 cc. of serum, depending upon the size of the patient and other factors preferably given intravenously although the intramuscular or subcutaneous route may be used. Transfusions of immune blood may be used as a substitute when available.

Management of subglottic edema becomes of paramount importance when there is dyspnea. Intravenous use of concentrated human plasma may solve this and tracheotomy may be avoided. The osmotic action of the hypertonic plasma protein withdraws the fluid of edema from the interstitial spaces of the subglottic tissues and tracheobronchial tree into the blood stream. Avoidance of laryngeal obstruction and tracheot-

omy also avoids serious sequela notably tracheobronchial crusting with obstruction. This in turn contributes enormously to shortening the convalescence. In cases which develop edema in spite of therapy, tracheotomy or intubation may become necessary. While Baum believed that intubation is the operation of choice especially early, a combination of both intubation and tracheotomy may frequently be of advantage to minimize tracheobronchial dryness. Humidification of the inspired air is very important in the prevention of the dryness of the tracheobronchial mucosa and the formation of crusts.

While experiences with *penicillin* have been few, it probably would be of little value if the primary invader is a virus; however, it has been used successfully to combat secondary infection. It also has been reported as acting favorably when instilled into the tracheotomic cannula.

**Magnetic Removal of Foreign Body.** A magnet to aid in the removal of magnetizable metallic substances both from the air and food passages was described by Eguen.<sup>8</sup> The magnet used in the tracheobronchial tree is cylindrical and is attached to a ureteral catheter which may be passed through the bronchoscope under fluoroscopic guidance. The magnet for use in the esophagus and stomach is attached to a tube which permits inflation of the stomach when desired. Unfortunately, many of the foreign bodies are not magnetizable and the field of usefulness of a magnet therefore is somewhat restricted. In spite of this, however, it has a definite field in foreign body removal.

**Pulmonary Abscess** While reports on pulmonary abscess in children are few, suggesting that the condition may be uncommon, D'Ingianni<sup>9</sup> expressed the opinion on the basis of his studies

that this cannot be substantiated. In a series of 417 cases of abscess of the lung, 64, or 10.5 per cent, occurred in children of thirteen years or younger, and of these 29 per cent were children under one year of age. It was found that abscesses on the right side were approximately twice as frequent as on the left and that the lower lobe was involved more frequently than the upper. The mortality rate was approximately the same irrespective of the side involved.

Opinions as to methods of treatment varied greatly. *Sulfonamides* were used in eight cases in this group with three improved and five deaths. *Pneumothorax* was attempted in one patient without improvement. The treatment was primarily symptomatic and only three were subjected to surgery.

References are made to the employment of *postural drainage*, *bronchoscopy*, *bronchography*, and also the use of *arsenicals* in the fusospirochetal type of abscess. The opinion was expressed that palliative forms of therapy are inadequate and that *extirpation* of the lesion seemed the more feasible plan of therapy.

In an analysis of 244 cases of pulmonary abscess, Valle<sup>10</sup> admitted that in spite of advances made in the treatment of other diseases of the lungs, the methods so far devised for the treatment of abscess were not wholly satisfactory.

It was interesting to note that in 27 per cent of cases, the abscess occurred either following tonsillectomy under ether anesthesia or abdominal operation under general anesthesia. Of thirty-six cases of abscess among children, 8, or 23 per cent, followed aspiration of a foreign body.

In view of its postoperative occurrence, they recommended that careful attention to the mouth and throat be given before contemplating operation

and that every effort be made to avoid aspiration of mouth secretions and vomitus into the tracheobronchial tree. If this has occurred, frequent aspiration of secretions and vomitus by nasal catheter from the tracheobronchial tree should be carried out during and immediately following any surgical procedure.

In treatment, nonsurgical methods excluding bronchoscopic aspiration have been largely discarded because of their ineffectiveness and the delay in the performance of surgical drainage. Penicillin seemed to be helpful in some cases. Postural drainage was given a fair trial in treatment and this procedure coupled with bronchoscopy sometimes resulted in a cure without surgical intervention.

Of the 244 cases, 92 per cent had either one or more bronchoscopies. They considered this as one of the most important features in the diagnosis and treatment and, in eighty patients treated only by bronchoscopy, forty-seven were improved. As a diagnostic procedure it is useful in localization of the abscess by revealing the draining bronchus. It is invaluable in making a differential diagnosis between uncomplicated pulmonary abscess and abscesses associated with carcinoma. In pulmonary abscess complicating foreign body bronchoscopy is considered imperative.

As a part of treatment bronchoscopy was of value in promoting drainage through the natural passages by keeping the bronchi open and thus facilitating postural drainage. Removal of granulation tissue also often was helpful. Patients in poor physical condition frequently were greatly improved by several bronchoscopic drainages so that later surgical drainage could be carried out with less hazards.

**Neoplasm of the Trachea**—Tumors of the trachea occur infrequently and there has not been observed a propor-

tionate increase when compared with the incidence of bronchogenic carcinoma. In reviewing a series of twenty-seven cases of neoplasm of the trachea, Tinney<sup>11</sup> and his associates emphasized the importance of early recognition. As a rule, the lesions are far advanced before a correct diagnosis is made and the prognosis therefore is poor. The most frequent and most important symptom observed was dyspnea produced by encroachment of the tumor, producing obstruction of the lumen of the trachea. This was observed in twenty-four cases (89 per cent) and was the initial symptom in twenty-two (81 per cent). Cough was observed in fifteen cases (56 per cent).

The best therapeutic results were secured in cases of cylindroma. These were treated by irradiation, using either *radium* or *roentgen rays* without or with diathermy. Carcinoma offered an extremely difficult therapeutic problem and no one form of treatment was found satisfactory. If situated in the upper portion of the trachea, the carcinoma was best handled by means of tracheal fissure and destruction of the tumor by *diathermy*. Carcinoma in the lower end of the trachea was best treated by diathermy through the bronchoscope. The implantation of radon in the tumor, although employed, probably was of questionable value.

In most cases death is caused by tracheal obstruction, hemorrhage, or secondary pulmonary suppuration.

**Bronchoscopy in Pulmonary Tuberculosis**—In a study of 279 patients with pulmonary tuberculosis, Tapia Acuna<sup>12</sup> found tuberculous lesions in 83, or 29.7 per cent, of the total group. This was not considered excessive when it was taken into consideration that bronchoscopy was performed because tracheobronchial lesions were suspected.

Granulomatous lesions were found in 52 cases. The left bronchus was involved in 46 instances (55.4 per cent). The frequency of lesions in the left bronchus suggested that infection results from prolonged contact of the mucosa with purulent secretions since drainage is less effective from the left side.

Different forms of local treatment were employed. *Diathermy* did not seem to give satisfactory results. Applications of a solution of *silver nitrate*, 10 to 30 per cent, and, in one instance, 50 per cent, were successful. The writer was agreed that *bronchoscopy* is of great aid to the phthisiologist and thoracic surgeon. It has many advantages and in his experience it did not constitute a danger in tuberculosis, there being no mortality observed which could be attributed to the introduction of the endoscopic tube or to manipulation of the tracheobronchial tree.

The frequent occurrence and serious implications of tuberculous tracheobronchitis, particularly when collapse therapy is contemplated, emphasized the need for bronchoscopic investigation of these cases, particularly if indications are present. While this probably is not generally recognized, there is an ever-increasing number of patients being examined and, in some institutions, routine bronchoscopy is performed on every patient admitted.

In a discussion of tuberculous tracheobronchitis, Wilson<sup>13</sup> divided the indications for bronchoscopy into clinical and roentgenological and considered them under these headings. The clinical and roentgen evidence of tuberculous bronchitis is based on the fact that in many of these cases there is narrowing of the bronchus with retention of secretion and, if these signs and symptoms are used as a guide in selecting patients, a high incidence of bronchial lesions will be discov-



ered. Among the contraindications are pulmonary hemorrhage, acute respiratory infection, and tuberculous laryngitis. The latter is considered an absolute contraindication except in cases of extreme emergency such as bronchial occlusion following thoracoplasty.

The question of local therapy has been a debatable point. Wilson employed a local application of *silver nitrate* in 30 per cent solution at intervals of two weeks, treatment being instituted as early as possible. He has never seen stenosis result from the employment of this strength of solution and agreed with many authors that any resulting fibrosis in the bronchus is the end result of the destruction of the bronchial structures by the tuberculous process itself and not from the use of silver nitrate. Local therapy is employed only to areas of ulceration and granulation tissue. No attempt is made to treat fibrous stenosis. In his experience, no method of therapy will effect any permanent dilatation. Temporary relief, however, may be secured by dilatation and aspiration of retained secretions. In the lesions that responded well, treatment was continued at intervals of two weeks until all evidence of activity had disappeared, but repeated examinations were performed for at least six months to determine any early recurrence.

Menendez<sup>14</sup> and his associates found tuberculous tracheobronchitis in 20 to 25 per cent of patients with pulmonary tuberculosis. This was found more often in women, particularly between twenty and thirty years of age. The early recognition of tracheobronchial lesions was emphasized, for treatment then can be promptly instituted and certain of the end results, namely cicatricial stenosis, may be avoided. In their experience, the fibrostenotic forms gave approximately a mortality rate of 50 per cent.

While there are certainly clinical symptoms and radiological signs, these are not sufficiently positive to permit a diagnosis without corroboration by bronchoscopy. In their experience, no complications to bronchoscopy have been observed. They believed, however, that biopsy is contraindicated in tuberculous lesions.

Certain of the indications for bronchoscopic investigation are discussed. Emphasis was placed on the occurrence of symptoms which suggest asthma. These invariably denoted the presence of a tracheobronchial lesion, although certain patients with tuberculosis may be allergic. Before considering such a patient as an asthmatic, bronchoscopic investigation is definitely indicated.

Local treatment, using *silver nitrate*, was considered the most effective plan in the acute stages of the tracheobronchial lesions. In the presence of bronchial stenosis, pneumothorax proved ineffective in many instances and at times was dangerous, so that a permanent type of collapse was probably preferable.

Although medical literature contains many reports on the employment of bronchoscopy in the diagnosis and treatment of pulmonary diseases, there are few which deal with the harmful effects of this procedure. Titcher<sup>15</sup> reported on a series of 361 bronchoscopic procedures performed in 214 patients, a majority of whom had pulmonary tuberculosis. Of 245 bronchoscopies performed on 147 patients with pulmonary tuberculosis, 103 bronchoscopies were followed by an initial febrile reaction during the first week and in 22 instances there was a rise of temperature after this time. In the latter group, roentgen examination revealed an extension of the tuberculous process in 4 patients. Of the 116 bronchoscopies that were performed in 67 patients with nontuberculous pulmonary

conditions, there was a rise in temperature during the first week in 37 cases and a later rise in 2 cases.

The initial rise in temperature probably could be explained in the majority of instances by the trauma of instrumentation and this appeared to be borne out by the similarity of the reactions in the tuberculous and the nontuberculous cases. The secondary rise was particularly important in tuberculous patients and appeared to be an indication either of a spread of the disease or further activation of it.

The only suggestion that could be offered to prevent further occurrences is a more careful selection of patients for bronchoscopy and doing the procedure with a minimum of trauma. Patients should be encouraged to clear the tracheobronchial tree of secretions as soon as possible after bronchoscopy since the disturbance of the cough reflex by the anesthetic may be a factor. It was therefore recommended that the minimal quantity necessary for the procedure be employed.

**Esophageal Obstruction.** Richardson<sup>16</sup> carried out experimental studies with caroid which contained papain, an enzyme similar to pepsin, to determine its ability to digest meat and employed it in the treatment of cases of obstruction of the esophagus due to meat impaction. He reported his results in seventeen cases. Caroid powder first was employed. Later it was placed in solution, using glycerine, then used with lactose and finally it was found that a 5 per cent solution of *papain* dissolved in a 10 per cent *alcoholic vehicle* was most satisfactory. Its ability to digest meat was not impaired and a stock solution could be made which could be kept for many weeks.

Before administering it, a roentgen study was made to confirm the diagno-

sis, to rule out the presence of bone and to determine the exact location of the foreign body. Fluoroscopy with and sometimes without a barium mixture gave the desired information. The patient then was given small quantities of the papain solution, depending upon his ability to swallow. One or 2 cc. administered every fifteen minutes usually yielded excellent results. A majority of the patients with esophageal obstruction were relieved within an hour and a half. In sixteen of the seventeen, prompt relief was secured. In the remaining patient, it was necessary to remove the foreign body instrumentally as the patient was unable to retain the solution in the esophagus.

#### Benign Tumors of the Esophagus

The symptoms of all esophageal lesions are so similar that they usually afford little differential diagnostic information. In their report on benign tumors of the esophagus, Adams and Hoover<sup>17</sup> found no helpful physical signs. Roentgenologic study with barium, however, brought out certain characteristic features of benign esophageal tumors. Esophagoscopic findings often are of little value, particularly if the tumor is intramural. Since these usually are covered by intact mucosa, a biopsy not only would give no information but would be contraindicated, particularly if surgical removal was shortly to be contemplated.

In one case, a polyp of the esophagus which was pedunculated, being 6.5 cm. in length and having its origin at the cricopharyngeus muscle, was removed esophagoscopically with the aid of a snare and diathermy. The patient made a satisfactory recovery.

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## GYNECOLOGY AND OBSTETRICS

### GYNECOLOGY

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#### PELVIS DISORDERS

##### Sulfonamide Therapy Gonococcal Infection

The value of *sulfonamide therapy* in gonococcal infection has been well established and proof of effectiveness of treatment has been based primarily upon results obtained from male patients. The part women can play in the spread of this infection makes it imperative that their treatment be evaluated. It is essential to determine: (1) To which sulfonamides these women respond most surely and promptly; (2) how long organisms may be harbored with few or no symptoms; (3) when the carrier state ends, and (4) whether so-called "drug-fast" strains are produced frequently.

Hesseltine<sup>1</sup> and his co-workers treated 1126 women with *sulfanilamide*, *sulfapyridine*, *sulfathiazole*, or *sulfadiazine*, the criteria for cure requiring that patients be observed at least two months following therapy before they could be discharged as cured. Only 575 patients treated were considered in this report as the remaining 551 were delinquent.

The diagnosis and cure were based on cultural studies. Fifty-one of the 575 patients were pregnant. Seventeen per cent were asymptomatic except for slight discharge. The infection was acute in 74 per cent and of these 18 per cent either already had or later developed salpingitis or Bartholin's abscesses. Four hundred and thirty patients, or 75 per cent, responded to one course of therapy and were discharged as cured and 145 had repeated or recurrent positive cultures and received further therapy.

*Sulfadiazine* was the drug of choice with 94 per cent cured; with *sulfathiazole*, 87 per cent; with *sulfapyridine*, 82 per cent, and with *sulfanilamide*, 71 per cent. Careful scrutiny of the patients who failed to respond to initial therapy revealed considerable information. Chronic infections responded to treatment as readily as did acute ones. Twenty-six per cent of the patients had chronic infections, while only six (16 per cent) of the thirty-eight patients who failed to respond to one drug had chronic infection. Patients with secondary complications responded about as well as did

other acute cases. Eighteen per cent of those with acute infections had secondary complications; eight, or 21 per cent, of the failures were in cases with secondary complications.

Infection in the pregnant patient was more resistant to sulfonamide therapy than in the nonpregnant patient. Eighteen per cent of the failures were in patients who were pregnant, whereas the pregnant patients comprised only about 9 per cent of the whole series. The failure rate of the whole series was only 7 per cent (38 of 575). From this study the authors conclude:

1. *Sulfadiazine* is the drug of choice in the treatment of gonococcal infection in women. *Sulfathiazole* is slightly less effective. Both drugs gave better results and were better tolerated by the patients than were *sulfanilamide* or *sulfapyridine*.

2. Diagnosis of gonorrhea and criteria of cure, wherever possible, should be based on cultural studies. Patients should be observed through at least one negative menstrual period and preferably two. Negative smears and cultures taken just following the menstrual period should be required. Considerable information is obtained from cultures taken during therapy.

3. The menstrual period is the best provocative test.

4. Complications of salpingitis or bartholinitis were not associated with more failures of therapy than acute uncomplicated cases.

5. Drug-fast strains were produced in the adult women in less than 1 per cent of the cases.

#### Penicillin Treatment of Sulfonamide-Resistant Infections

The present report<sup>2</sup> is based upon an analysis of results obtained in 108 hospitalized female patients suffering from

gonococcal infections, who were treated with varying amounts of penicillin.

The urethra alone was found to be infected in 3 cases; the cervix alone in 39. A concurrent urethral and cervical infection was present in 66 women. Adnexal involvement was observed in 34 patients, although it was of a severe character only in exceptional cases. This paucity of acute adnexal disease may have been due to the long duration of the infection which averaged seventy days, and to the fact that the majority of patients had already received two or more courses of sulfonamide in addition to other supportive therapy. One patient suffered from diffuse peritonitis. Another developed arthritis of the elbow during the course of penicillin treatment. Pregnancy ranging from three to nine months was present in six patients.

Of the 108 patients treated, 101 had failed to respond to at least two courses of various *sulfonamides*; the remaining seven patients showed a definite sensitivity to *sulfonamide compounds*.

Of the total of 108 patients, 90 promptly became bacteriologically negative after one course of *penicillin* and 9 by the administration of a second course of *penicillin*. The results obtained by the administration of various amounts of *penicillin* point to the fact that a minimum total dosage of 100,000 I.U., injected intramuscularly in divided doses, is both necessary and sufficient for bacteriologic cure. The minimum total period of time required for successful therapy was found to be six hours. Smaller doses of penicillin and shorter total time treatment were adequate in individual cases, but this type of therapy is not to be recommended.

Urethral discharge following penicillin therapy disappeared within a week, cervical discharge was not appreciably affected in the majority of cases. Acute

symptoms and signs of adnexal involvement subsided within one to two weeks after penicillin treatment. There were three cases which had an exacerbation of the adnexal involvement immediately following the use of penicillin, and one patient developed salpingitis following therapy.

After their discharge from the hospital, 81 of the total of 108 women were followed for an average period of 43.6 days, during which an average of 3.5 examinations were performed. Fifteen patients were found gonococcus positive after an average follow-up of 51.7 days. The authors assume that these patients represent reinfection rather than recurrences. There were no serious toxic symptoms present in this entire group of 108 patients treated with penicillin.

#### **Lactobacillus Therapy—Vaginitis Due to Trichomonas**

The idea of trying to free the vagina of trichomonads by implanting lactic acid-forming bacilli occurred to the authors<sup>3</sup> after a careful study of the normal defensive mechanism of the vagina which depends primarily on the three following conditions: First, that the vaginal secretion remains at its normal low pH; second, that the Döderlein or vaginal lactobacilli are present in sufficient numbers to form lactic acid; and, finally, that there is sufficient carbohydrate, perhaps in the form of glycogen, in the vaginal epithelial cells or spaces between them to afford adequate nourishment for the continued growth and activity of the Döderlein bacilli.

In 1941 the authors reported a series of fifty cases treated with viable lactic acid-forming bacilli. This treatment usually gave quick relief from symptoms, and, in a great majority of cases, the vagina became free of trichomonads and remained so. The tablets were prepared

from Hansen's strain of *Lactobacillus bulgaricus* and was obtained from the United States Department of Agriculture.

This report is based on a second series of seventy cases treated in this manner. The method at present advised is the following:

As soon as the diagnosis is made, the cervix is inspected for complicating endocervicitis, and Skene's and Bartholin's glands inspected for possible involvement. The vagina is then dried with cotton and two *lactobacillus tablets* inserted high in the vagina in the posterior fornix behind the cervix. The vaginal orifice is then plugged with a tampon of nonabsorbent cotton. When the patient returns on the next day, the tampon is removed, material taken from the vagina for microscopic study, and the treatment of the preceding day is repeated. This office treatment is repeated for five days. The patient is then told to insert two tablets high in the vagina each night for two to four weeks and longer if necessary. Douches are taken only if she becomes uncomfortable from unabsorbed particles of the tablets coming out of the vagina and causing irritation. If a douche is used, white vinegar is recommended in a strength of two to four tablespoons to two quarts of water.

In sixty-four of the seventy patients treated, wet preparations were negative after two weeks of treatment, and all but three of the women stated that their symptoms had disappeared by that time. Four of the six patients became free of organisms after three months. The authors feel their results have been very satisfactory and are of the opinion that most of the failures reported to them by other physicians can be explained by two factors. First, the physicians recommended daily vaginal douches which defeats the purpose of the method of treatment; second, they have not insisted that the treatment be continued through the menstrual period.

#### **Treatment—Thrombophlebitis**

The authors, Yahr and Reich,<sup>4</sup> point out that until recently little change has been made in the therapy of thrombo-

phlebitis, and little except symptomatic treatment has been offered. During the last few years anticoagulant therapy has gained prominence in the treatment of thrombophlebitis and its associated complications.

*Heparin* was used after its purification by Murray and Best. There were, however, certain difficulties regarding its use: It is expensive; it must be given intravenously; its results are unpredictable; its margin of safety is narrow, and it requires frequent determination of coagulation be made during its use.

*Dicumarol* has been used since 1940. This substance does not present the same difficulties inherent in the use of *heparin*. The results of treatment with this substance have been inconclusive. Some investigators reporting favorably, others feeling that anticoagulants should not be used in the treatment of thrombophlebitis. Neither the size of the series of the investigation nor the success achieved seems to justify definite statements as to its value.

The authors have applied a uniform type of therapy to sixty-seven cases of thrombophlebitis and its complications, divided into four groups on an anatomical basis. (1) Superficial phlebitis; (2) deep phlebitis; (3) superficial and deep; (4) pulmonary embolization with or without a demonstrable phlebotic site.

Prothrombin times were done daily according to the method of Shapiro.

In the *superficial phlebitis* group there were eleven cases; eight female and three male. Four were postpartum, two antepartum, and five were cases of phlebitis of long standing. *Dicumarol* was administered in sufficient dosage to keep the prothrombin time prolonged to double the normal value of that particular patient.

*Wet boric acid dressings* were applied continuously to the affected area

and 0.03 gm. ( $\frac{1}{2}$  grain) *papaverine* was given at irregular intervals for excessive pain. The average number of days in bed was ten, and the criteria taken for remission of the attack were diminution or disappearance of pain or tenderness over the affected areas. *Dicumarol* was discontinued on disappearance of pain and tenderness over affected area and normal temperature and pulse. The patient was then allowed out of bed, permitted active motion with the application of an *Ace bandage*. The average total dose of drug was 1000 mg.

These patients were followed for an average of from six to ten months and no recurrences reported to date. One of the antepartum cases in which treatment was started at the seventh month was entirely free of pain on the fourth day after injections were started. She was asymptomatic on the tenth day and allowed out of bed. She developed no postpartum phlebitis and there was no untoward effect on the baby. The other patient also showed good response but had not reached term at the time of this report. They are encouraged to continue the use in these cases because of long omissions and rapidity of response. In none of these cases was there an attempt to control infection *per se* with either chemotherapy or other antiseptic agents.

**Deep Phlebitis** This group contains twenty-seven cases: nineteen females and eight males. Four were postpartum, sixteen were postoperative and the remainder were without definite etiological factor. *Dicumarol* was begun as soon as the diagnosis was made. The involved extremity was elevated, protected by a cradle and an icebag applied at the point of tenderness. The largest dose was 2300 mg., the smallest 500 mg. The method of administration was the same as described and prothrombin times were done daily. The criteria for

remission were normal temperature and pulse, lack of tenderness over the affected veins as well as loss of pain and marked decrease in the amount of swelling. The prothrombin time was kept within the therapeutic range for at least twenty-four hours after patient got out of bed. The average time in bed was 10.5 days with a range of five to twenty-three days. Pain usually subsided within twenty-four hours after the patient's prothrombin time was in the therapeutic range. No sedation was necessary. There were no episodes of pulmonary embolization, no untoward effects from dicumarol occurred.

#### *Superficial and Deep Phlebitis—*

There were nine cases in this group, seven female, and two male. Five were postoperative hysterectomies, one was an antepartum patient in her eighth month. The regimen followed in these cases was the administration of *dicumarol*, elevation of the leg, wet boric acid dressings to the affected area, and papaverine in doses of  $\frac{1}{2}$  grain every four hours for pain. The largest total dose administered in these cases was 1400 mg. and the smallest 600 mg. The average stay in bed was 14.7 days with a range of seven to twenty-five days. There were no complications referable to embolic phenomena nor were there any toxic effects due to dicumarol.

**Pulmonary Embolization** — This group includes ten patients, seven female and three male. There were no symptoms and history of phlebitis in any of these cases, the first symptoms being those referable to embolus of the lung. Eight patients had one and three had two pulmonary emboli. These patients fit into the group described by Homans as silent thrombophlebitis in which the first symptom is referable to the embolus and not to the original phlebitic site. In eight of the patients, the condi-

tions were postoperative, each patient having had some type of pelvic operation.

All patients were treated in the same fashion. *Dicumarol* was started as soon as the patient was seen and continued in sufficient doses to keep the prothrombin time elevated to twice its normal value. The only other therapy was an adequate amount of sedation to control pain.

While under therapy, none of these patients had any further episodes of pulmonary emboli. They remained in bed an average of fourteen days, the longest time being twenty, the shortest thirteen. One patient was found to be resistant to the ordinary dose of dicumarol. The prothrombin time in this case was never raised above twenty-five seconds. When a second group of pulmonary emboli occurred, she was treated with heparin.

The results were uniform while under treatment. There were no toxic effects due to *dicumarol*, and the drug was administered and controlled without difficulty.

**Summary**—The treatment with *dicumarol* had the following effects:

The diminution in the length of time of treatment, the lack of complications referable to phlebitis as well as dicumarol. None of these cases while under treatment or in the posttreatment period developed emboli. In those cases having had previous embolic phenomena, there was no further evidence of it after therapy was begun. In none of the sixty-seven patients did other foci of thrombophlebitis occur either in the treatment or posttreatment periods.

Pain is markedly decreased in direct relationship to the initial elevation of the prothrombin time. *Dicumarol* appears to have a wider margin of safety than other forms of anticoagulants. The prothrombin time in these cases varied be-

tween 15 and 70 seconds. Despite this, there was no evidence of hemorrhagic diatheses. The initial doses consisted of 300 mg. the first day, and 200 mg. the second day. Following these doses, from 50 to 200 mg. in twenty-four hours were given. The guide to the proper dose was the prothrombin time. If after 500 mg. the prothrombin time had risen to double its initial value, no further dose was given. If it was rising rapidly but had not reached the therapeutic range, *i. e.*, double its initial value, no dose was given. If there was no rise, or it was rising slowly, from 50 to 200 mg. was given, depending upon the initial elevation. This same scheme was followed throughout the course. The third dose in their cases was almost always 100 mg.

*Dicumarol* was begun during various intervals of the postoperative period, but in no case was it necessary to begin treatment before the third postoperative day. As far as could be determined there was no interference with wound healing and no hematomas developed. In the obstetrical cases, nineteen of which were postpartum, there was no increased vaginal bleeding nor was the postpartum period affected in any way. In these cases *dicumarol* was begun as early as twenty-four hours following delivery. Only one resistant case was encountered and her prothrombin time did not go above 20 seconds despite a total dosage of 2100 mg.

### Vaginal Smears—Diagnosis of Early Malignancy

**A Preliminary Report**—Any procedure that facilitates the early diagnosis of a disease as devastating as carcinoma of the uterus deserves serious consideration and extensive trial. Papanicolaou and his associates have opened a field that may eventually revolutionize the story of pelvic carcinoma in women. The

study of vaginal smear should be considered as an accessory or preliminary method of diagnosis, and the actual demonstration of malignant cells in the biopsy specimen should be the basis for decision as to the method of therapy.

Certain characteristic features are recognized as being common to vaginal smears from both fundal and cervical carcinoma. These are evidenced to the experienced investigator with low power microscopic examination, and may be enumerated as follows:

1. Large numbers of polymorphonuclear leukocytes are commonly found. These tend to be clumped as well as scattered and many are seen engulfed by other cells.

2. Bacteria are numerous.

3. Red blood cells are found in varying numbers, even in the early stages. Generally, they have lost their clear cut outlines, and appear crenated, degenerated or as shadow forms. The finding of red blood cells is considered so important that in their absence one should hesitate to render a positive diagnosis of malignancy. There are, however, exceptional instances of some very early cases in which red blood cells are not found.

4. The degree of cornification is frequently higher than in smears from non-malignant cases, and it is common to find the cancer cells themselves cornified.

5. Histiocytes, appearing as single cells, are very common. They are large, foamy, often multinucleated cells, whose cytoplasm engulfs leukocytes, cellular debris, and degenerated red blood cells.

6. Bizarre cellular forms are found of varied size and shape. The cytoplasm is hyperchromatic and contains deeply staining granules. Vacuoles are frequently found, and these often contain ingested cellular debris. The nuclei of these cells are dense, granular, irregular



in form, and may show prophases or arrested phases of mitosis. These are the malignant cells which determine the final diagnosis.

The conclusions in this study are based upon 427 cases, 245 patients were seen in the Strang Clinic and 182 in the Gynecological - Endocrine Clinic of the New York Post-Graduate Hospital. In 91 cases, a diagnosis of malignancy was made from the vaginal smears, of which 82 were confirmed by biopsy or curettage. The diagnosis of carcinoma of the cervix was made in 53 instances; carcinoma of the fundus in 37, and sarcoma of the cervix in 1 case. Confirmation of the vaginal smear diagnosis was obtained through tissue study in all but 9 instances. In 7 cases, a negative smear diagnosis was reported which was subsequently proved incorrect when curettings were submitted.

The apparent high incidence of malignancy in the group of patients examined is due to the fact that of the total number of cases approximately 57 per cent were observed at the Strang Clinics, which are exclusively confined to the study of new growths. The fact that there were three instances of very early neoplasms discovered during routine examinations of endocrine patients is of paramount importance, for it definitely illustrates the advantages of routine vaginal smear.<sup>5</sup>

### Perineum

**Laceration and Repair** -- Phaneuf<sup>6</sup> divides perineal lacerations due to childbirth into recent, occurring at time of labor, and old lacerations. The former are divided into tears of first, second, and third degree tears. The second group comprise gynecological tears and are divided into incomplete and complete, the latter involving sphincter of the rectum and rectovaginal septum. Another

form of injury is the relaxed vaginal outlet in which the damage to fascia and muscles was not associated with tear of the skin and mucosa of the vagina, but was subcutaneous, and produces a bulging called a rectocele.

The repair operations may be immediate or remote, depending on the condition of the patient at the time of delivery. Recent improvements in these operations are due to the use of fine catgut. The pelvic floor layers are approximated without tension, using fine catgut or silk, and continuous or interrupted sutures.

Intermediate repair of birth injuries is seldom indicated. It is carried out about ten days after childbirth. The parts are prepared with germicidal solutions. Granulations are curetted from the torn edges.

Late repair of laceration is best done not sooner than three months after labor and is frequently combined with other minor or major gynecologic procedures, and operations including vaginal or abdominal hysterectomy. Often these repairs are done twenty-five or even fifty years after the original injury occurred.

Preoperative preparation consists of *saline cathartic* two nights before entering the hospital followed by light diet. External genitalia shaved and scrubbed with green soap the day before operation and rinsed with sterile water and *potassium mercuric iodide solution*, 1:1000. Vaginal douche, 2 drams, compound zinc sulfate powder in 2 quarts of water. A soapsuds enema on the afternoon or evening of the day before operation. After the patient is anesthetized in the operating room, the parts are cleaned with ether and painted with *tincture of zephiran* inside and outside the vagina. If much vaginal discharge is present, the vulva and vagina are scrubbed again with green soap in addition.

Phaneuf uses a Friedman or Gelpi retractor to free the hands of assistants for other duties. A side-to-side perineotomy at the mucocutaneous junction. Vagina and rectum are separated by sharp and blunt (gauze-covered finger) dissection. The crura of the pubococcygei muscles are united by three interrupted chromic No. 0 catgut. The urogenital diaphragm is the second layer and includes the deep transverse perinei muscles and their fascia. The same suture material is used and the three sutures are left untied. The redundancy of the posterior vaginal wall is removed and the defect closed with interrupted sutures of catgut No. 0. Colles' fascia is approximated with running double 00. Redundant skin at the base of the wound is resected. The vagina is packed with iodoform gauze on a tape to facilitate removal in twenty-four hours.

**Morphine** and **codeine** are used for pain. Suture lines are painted with **zephiran** after each bowel movement or urination. The **zinc sulfate** douche is given daily after forty-eight hours. They are carefully catheterized as necessary. The bowels are moved on the third postoperative day.

Phaneuf reports on 2328 personal cases, of which 1556 gynecologic or secondary repairs and 772 obstetric or primary repairs. Of the former there were:

Perineorrhaphy for incomplete laceration.	1448
Perineorrhaphy for complete laceration..	101
Plastic operation to enlarge the vagina....	6
Excision of a sinus in perineum.....	1
Obstetric repairs:	1556
Episiotomy:	
Right .....	261
Left .....	51
Median .....	82
Bilateral .....	2
Lacerations:	
First and second degree.....	367
Third degree .....	9
	<hr/> 772

All cases had a good postoperative result as far as the perineorrhaphy healing was concerned.

There were fourteen gynecologic deaths and two obstetric. From an analysis of the cases reported here, it would seem that the perineorrhaphy had little to do with the fatal outcome, but were due to the associated major procedure undertaken at the same time.

### Androgenic Therapy in Malignant Disease of the Female Genitalia

**Preliminary Report** In the light of laboratory and clinical studies, and in view of the successful application in clinical urology in the treatment of prostatic carcinomas by the use of **testosterone propionate**, Abel<sup>7</sup> was of the opinion that an investigation of the possible value of male hormone in the treatment of malignancies in the female genital tract seemed warranted. If by the administration of **testosterone** the depressing effect on the pituitary would diminish the amount of sex-stimulating hormone, and if such administration is without effect upon the heterologous secondary female organs, it seemed not unreasonable to believe that retardation, even possible regression, of the malignant growth might occur in a manner comparable to the effect of estrogens on prostatic growths.

Patients were selected for therapy who failed to respond to orthodox forms of treatment, and for whom, it was felt, nothing more could be accomplished. A generous dose of **testosterone propionate** was arbitrarily chosen. One hundred forty to 150 mg. were given daily either orally or intramuscularly.

The first five patients, including three carcinomas of the cervix and two carcinomas of the corpus, have been receiving **testosterone propionate** for ten months. All the patients have shown striking improvement in morale with a feeling of

well-being bordering at times on euphoria. There has been a definite improvement of menopausal symptoms, such as nervousness, insomnia, headache, depression, and, in most cases, hot flashes. Increased libido has been consistent and marked. With the arbitrary dosage used, masculinizing symptoms appeared in all patients and have included hypertrophy of the clitoris, development of a beard, and voice change. Acneform eruptions have occurred in three of the original five patients and in many subsequent cases. Vaginal smears have tended toward the atrophic state and have changed little during treatment. In one patient some suggestion of cornification was seen from the beginning. To the present time, there is nothing to indicate any regression or even retardation of the malignant process in manner comparable to the effect obtained in estrogenic treatment of prostatic carcinomas. In one of the original cases, and in two subsequent cases, metastatic lesions have been seen to progress during the course of treatment. Abel is of the opinion that the feeling of well-being, increase in morale, and increased libido experienced in all cases warrants the administration of male hormone in this unfortunate group of patients.

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## MENOPAUSE

### Postmenopausal Pruritus Vulvae

Pruritus vulvae in the postmenopausal woman poses a clinical problem of the greatest magnitude. It is frequently encountered, is extremely discomforting to the patient, and is seldom handled successfully. Postmenopausal pruritus vulvae differs from the pruritus vulvae of the less mature woman in several respects, the most important being the relative infrequency of specific infections and the introduction of the atrophy

process in the external genitalia. After pediculosis pubis, diabetes mellitus, and specific local skin diseases have been eliminated, the physician should approach the problem with the philosophy that any area of skin can be responsible for the sensation of itching if the proper combination of skin irritation and receptiveness to that irritation is present.

It becomes apparent that the presence and source of irritating discharges must be sought for and evaluated. To this end, incessant wetting of the labia by urine of the incontinent woman is of importance. Vaginal discharges are the chief causes of vulvar irritation. The principal types of vaginitis encountered are the *Trichomonas vaginilis*, *Monilia*, and senile ones. It is the senile vaginitis most frequently encountered in the menopausal woman. The appearance of the vagina makes the diagnosis. Vaginal smear will corroborate the diagnosis, revealing little evidence of cornification of any of the epithelial cells; a moderate number of cells from the basal layers of epithelium is present and an abundance of leukocytes "dirties" the smear. This type of vaginitis yields readily to ordinary astringent tamponades and cleansing douches. Relief is obtained faster if estrogenic suppositories are employed at night before retiring.

Cinberg<sup>8</sup> is of the opinion that there are three types of pathology in pruritus: Atrophy, lichenification, and leukoplakia. He refuses to accept the term "kraurosis vulvae" as a clinical entity. These are common etiological factors in most cases of postmenopausal pruritus vulvae, and the response of the skin to these factors varies with the individual. The varied macroscopic and microscopic pictures one encounters in these cases are merely the resultants of the patient's capacity and manner of response to the same set

of stimuli. They are not different disease processes.

In the therapy of *postmenopausal pruritus vulvae*, Cinberg recommends avoidance of irritating an already irritated skin. This is accomplished by directing the patient to keep the affected area constantly covered with a thick coating of bland ointment. A base of *petrolatum alba* with 20 per cent *starch* and 30 per cent *zinc oxide* is an ideal preparation. This crème is kept on the vulva for the minimum of three weeks, and the patient may cover it with squares of gauze to protect her clothing. As the salve wears off, more is added. The patient may bathe as often as she desires, but she is not to attempt to clean off the salve. After her bath, she replaces the ointment washed away.

It is inadvisable to incorporate anti-pruritics in the salve. While they may afford temporary relief, they soon become ineffective, and all of them are irritants to a degree. The constant application of the bland ointment protects the vulval tissues from all irritants and gives them the opportunity of coping with the dermal infection. Scratching is reduced considerably. After three weeks, as the pruritus abates, the use of the ointment may be restricted to nights only. The salve may be removed in the daytime, by means of cottonseed, mineral, or salad oil. Soap and water may not be used.

In addition to protecting the skin from infection and irritation, attention should be directed to increase the resistance of the skin. To this end Cinberg employs large doses of *vitamin A* in the form of *concentrated fish oils*. Since senile vaginitis is not the chief cause of postmenopausal pruritus vulvae, estrogens are of little or no value and have no effect on the skin. *Androgens*, on the other hand, have proved effective

on the skin. *Testosterone* dilates skin blood vessels, increases the blood's content of oxyhemoglobin, and stimulates the blood flow. Since biopsies reveal an inflammatory process in the derma, *androgen* should be of value. Cinberg uses a preparation containing 2 mg. of *testosterone propionate* to the gram of *ointment*. Cinberg is of the opinion that roentgen ray is not indicated in the treatment of postmenopausal pruritus vulvae. In his hands local infection of alcohol, histamine, or a combination of procaine and benzyl alcohol have not been satisfactory.

During the past six years, 100 cases of postmenopausal pruritus vulvae have been treated, but only 14 cases form the basis of this study. Five of the patients had leukoplakia of the vulva. The treatment was successful in all 14 cases of severe pruritus in which pre-therapy and posttherapy vulva biopsies were obtained.

### Androgen Therapy

**Menopausal Symptoms in Cancer Patients**—Cinberg<sup>10</sup> has been dissatisfied with the use of *stilbestrol* in a certain group of menopausal patients in whom it was believed the stimulating effect of *estrogen* was contraindicated. This includes those patients who have been treated for some form of cancer of the reproductive organs and also some of those in whom *estrogen therapy* has provoked uterine bleeding. Those individuals who have already demonstrated the responsiveness of one of the reproductive organs to whatever abnormal stimulus develops carcinoma would seem especially unfavorable subjects in whom to administer a cell proliferating substance like *estrogen*.

Twenty four patients with histories of neoplastic disease or dysfunctional bleeding were treated for the relief of

menopausal symptoms. Twenty mg. of *methyl testosterone* were administered daily by mouth for four weeks; then 10 mg. daily for two weeks thereafter. *Androgen therapy* had strikingly benefited the vasomotor symptoms of the menopause in twenty-three of the twenty-four patients. Many patients experienced a feeling of stimulation and general well-being. No untoward reaction of significant degree was seen in this series of patients.

In summary, the author urges the use of *androgens* rather than estrogens for patients requiring endocrine therapy in the following groups: (*a*) Patients who have been treated for cancer of the reproductive tract or breast; (*b*) patients who have been treated for abnormal uterine bleeding during the climacteric; (*c*) patients who have developed uterine bleeding while under therapy with estrogenic substances; (*d*) patients who require endocrine therapy for vasomotor symptoms before their menses have completely ceased; (*e*) patients who have become addicted to stilbestrol by long-continued usage.

### Vitamin E in Menopause

**Preliminary Report of Experimental and Clinical Study** — Christy,<sup>10</sup> being impressed with the favorable response obtained from vitamin E therapy in "war amenorrhea," and by our incomplete knowledge about the chemistry and physiology of this substance, began to investigate the effect or potentialities of vitamin E in the menopause. Therapy with estrogens in a large number of his cases, due to the cancerous nature of the lesion, was wholly contraindicated. In this study of six months' duration, vitamin E in 10-mg. tablet form as *ephynal acetate*, a synthetic preparation, was given by mouth to twenty-five patients varying from twenty-

two to fifty-five years of age. Of this group, twelve had carcinoma of the cervix, one had adenocarcinoma of the fundus, one had malignant leiomyoma and sarcoma of the uterus, six had fibroids, one had carcinoma of the ovary, one had hemangioendothelioma of the parametrium, one had postmenopausal bleeding after estrogen therapy, one had dysfunctional uterine bleeding due to endocrine disorder, and one had endometriosis. No patient was treated who did not complain of severe symptoms of vasomotor instability.

The amount of drugs taken varied from 10 to 30 mg. a day, depending upon the degree of severity of symptoms, over periods of from one to six weeks. Of the twenty-five patients, one suffered from symptoms of natural menopause, five from surgical and irradiation menopause, eleven from x-ray and radium menopause, eight from radium menopause. Of these twenty-five patients, seven report complete relief from symptoms on dosages of 10 to 20 mg. daily over periods of from one to three weeks. Sixteen patients reported very marked relief on 10 to 20 mg. daily over periods of from two to six weeks. Two patients interrupted treatment.

The clinical response was based largely on subjective findings. In a few instances, vaginal smears and endometrial biopsies revealed that vitamin E induced no change in the vaginal mucosa and endometrium. The chief advantage of vitamin E over estrogen is in the fact that vitamin E is free of any stimulative effect or change on the genital system or in the parenchyma of the breast. It plays no possible carcinogenic rôle as the estrogens may do, and due to the latter factor, vitamin E can be used fully in menopausal patients suffering from neoplastic disease.

## FALLOPIAN TUBE

### The Spread of Uterine and Ovarian Carcinoma

The rôle that the fallopian tube has played in the spread of carcinoma of the ovary to the uterine fundus, and, conversely, in the transmission of the carcinoma of the endometrium to the ovary has long been a point of controversy. Lynch and Dockerty<sup>11</sup> have carefully studied 113 cases of carcinoma of the uterus or ovary, or both of these, all in which it was possible to study in a satisfactory manner the spread of carcinoma from the uterus to the ovary or from the ovary to the uterus. In 51, or 44 per cent, of the cases, the lesion arose in the ovary and involved the fallopian tube, and in 12 cases it arose primarily in the fundus of the uterus and involved a fallopian tube. In 20, or 18 per cent, of the cases, the lesion involved the ovaries, endometrium, and tubes. In 12 of these cases, the primary site of the lesion was in the ovary; in 6 cases it was in the uterine fundus, and in 2 cases the primary site was doubtful. In 30 cases, ovarian and endometrial carcinoma coexisted without evidence of tubal lesion. The primary growth was uterine in 12 cases and ovarian in 13. In 5 cases, the site of the primary lesions was doubtful and the possibility of two independent sites of origin could not be excluded entirely.

Anatomic studies have demonstrated the existence of interconnecting links in the lymphatic drainage of the uterus, tubes, and ovaries. It is not surprising, therefore, that the author's studies have shown direct extension and lymphatic permeation as the chief pathways in the dissemination of carcinoma from one to the other aforementioned structures. The surprising small number of cases in which such modes of transmission did

not hold revolve around the question: Does carcinoma spread by the lumen of an intact fallopian tube?

Approximately 6 per cent of ovarian carcinomas metastasized to the endometrium and examination of curetted material occasionally revealed the extra-uterine site of the primary growth. Conversely, about 4 per cent of operable carcinoma of the uterine fundus eventually involved the ovary or ovaries. In both circumstances, the fallopian tube seemed to act as the intermediary host to the malignant cells. In only 1.4 per cent of cases did it serve in the capacity of a passive conduit, and in only 0.4 per cent was the direction of the flow reversed, namely, from uterus to ovary.

The inescapable conclusion from these studies is that carcinoma may spread from the uterus to the ovaries or *vice versa*. In the majority of cases, the spread is by direct extension, or by lymphatic extension, or by lymphatic permeation alone or combined, and, frequently, with simultaneous involvement of the fallopian tube as an intermediary stage in the process. In a minority of these cases, viable malignant cells may spread through the lumen of the fallopian tube, usually without becoming implanted on its mucosa. From a practical standpoint, little risk was indicated for the production of ovarian or abdominal implantation in curetting a uterus which is the site of a malignant lesion, prior to the insertion of radium.

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## OVARIES

### Hypo-ovarianism

**Treatment.** This report is a summary of a continuation of therapy on a series of 116 cases treated by the authors over a five-year period. The patients studied fell into four different categories:

(1) Patients with deficient sexual maturation whose menarches had not occurred. (2) Patients with infrequent and/or scanty bleeding. (3) Patients with prolonged and/or excessive bleeding. (4) Patients with ovarian sterility; this latter group comprised two subgroups: (a) Patients whose bleeding was associated with interval or estrogenic endometriums, who had anovulatory bleeding (fourteen patients), and (b) patients whose bleeding occurred from immature progestational endometriums (fifty in number).

The therapeutic schedules used in these studies are summarized as follows:

**Hemostasis**—The average daily dosage of *estrogen* employed for hemostasis is represented by 6 mg. of *diethylstilbestrol* or its equivalent in *estrone sulfate*. After hemostasis was obtained, *estrogen therapy* at the same dosage level was maintained for twenty days.

**Cyclic Estrogen Therapy**—Cyclic estrogen therapy was begun on the third to fifth day of the cycle and continued for twenty days, when it was withdrawn, or earlier if bleeding occurred. It was resumed on the third to fifth day of the cycle and kept up for two to three months.

**Cyclic Estrogen-Progesterone Therapy**—This therapy was started on the fifth day of the cycle. *Estrogen* was given orally and in daily dosages represented by 3 mg. of *diethylstilbestrol* for twenty days. During the last ten days of this treatment, the patient received orally and daily 60 mg. of *anhydrohydroxy-progesterone*.

**One - Two Cyclic Gonadotropic Therapy**—Therapy was initiated on the fifth day of the cycle after testing for allergy. From the fifth through the fourteenth days of the cycle, patients received intramuscularly and daily 400 international units of *equine gonado-*

*tropin*. From the fifteenth through the twenty-fourth days of the cycle, patients received intramuscularly and daily 500 international units of *chorionic gonadotropin*.

A total of 116 hypo-ovarian patients, whose ages placed them in the adolescent or reproductive epochs, was treated by the sequential and cyclic administration of *equine* and *chorionic gonadotropins*. The following results were obtained:

1. Only one of seven patients with deficient sexual maturation and non-occurrence of menarche yielded a progestational endometrium during therapy.

2. Four of thirteen patients, or 30.8 per cent, with infrequent and/or scanty estrogenic uterine bleeding yielded progestational endometriums during therapy.

3. Fifteen of thirty-one patients, or 48.5 per cent, with prolonged and/or excessive estrogenic bleeding yielded progestational endometriums during therapy.

4. Seven of fourteen patients, or 50 per cent, with cyclic estrogenic bleeding and ovarian sterility yielded positive responses, including four pregnancies during therapy.

5. Nine of fifty patients, or 18 per cent, with cyclic bleeding from immature progestational endometriums became pregnant during therapy.

From these results, Hamblen and Davis<sup>12</sup> draw the following conclusions:

1. Patients with hypoenestrogenism respond poorly to this system of gonadotropic therapy.

2. Patients with anovulatory ovarian failure without hypoenestrogenism respond well to this system of therapy; a total of 44.8 per cent yielded progestational endometriums.

3. A small percentage (18 per cent) of sterile women, whose bleeding from immature progestational endometriums constitutes the only significant finding

upon their surveys or those of their husbands, become pregnant when treated with one-two cycle gonadotropic therapy.

### Amenorrhea, Oligomenorrhea, and Anovulomenorrhea

**Studies**—Twenty-three patients with clinically hypofunctional ovarian activity were studied. These comprised three cases of primary amenorrhea, eleven of secondary amenorrhea, eight of oligomenorrhea, and one of cyclic anovulomenorrhea. Adjuvant therapy with *equine gonadotropin* was instituted. This hormone failed to establish menstruation in three cases of primary amenorrhea. Of the eleven cases of secondary amenorrhea, ovulation was apparently stimulated in two, although the result in one was open to serious question. Only one patient continued to have regular menses. In the seven cases of oligomenorrhea, *equine gonadotropin* apparently restored cyclic menses in one but failed to stimulate an ovulatory response in any. In the one case of regular anovulomenorrhea, *equine gonadotropin* was ineffectual. Nine of these twenty-two cases were later "salvaged" with an adequate diet and, usually, thyroid extract.

Abarbanel and Leatham<sup>13</sup> concluded the following from their investigations:

1. Clinically, *equine gonadotropin* proved to be a rather ineffectual stimulant to the abnormally functioning or hypofunctioning human ovary as far as the restoration of normal cyclic metabolism and the reappearance of regular menstrual rhythm were concerned.

2. *Equine gonadotropin* produced similarly poor results in stimulating an ovulatory response in patients with clinically hypofunctioning or abnormally functioning ovaries.

3. The principle of heterogenous substitutive therapy with *equine gonado-*

*tropin* may yield far greater harm than any temporary good. The possible harmful results of therapy with *equine gonadotropin* are (a) a gonadotoxic effect on the ovary as evidenced by abnormal stimulation or marked delay in appearance of the next menses; (b) development of antagonistic (antigonadotropic?) substances with neutralization of subsequent injections of *equine gonadotropin*; (c) development of allergic manifestations, which may be severe in spite of negative skin tests; (d) sensitization of the patient to other as yet unknown components of horse serum.

4. The principle of physiologic stimulative therapy by means of a nutritionally balanced diet and *desiccated thyroid extract* is far more rational and far more efficacious both on theoretical considerations and on the clinical results obtained.

### Tumors

**Teratoma**—Curtis<sup>14</sup> points out that teratoma while appearing in other organs of the body is predominantly ovarian in location. It is a compact solid mass of rapidly growing tissue frequently wholly undifferentiated corresponding to various stages of fetal development and revealing only isolated tendency to more completely developed organlike formation. Like a dermoid, all three germ layers are represented, the differences lie in the tissue of origin and in the fact that dermoids are comprised of mature tissues whereas a teratoma consists of embryonal elements.

Opinions differ as to the malignancy of teratoma. It is a growth characterized by great proliferation not sarcomatous or carcinomatous but inherent in the cells that constitute it, and there is topographical confusion. It should be regarded as potentially malignant in all cases.

Grossly, the tumors are usually of the size of a man's head, are peduncu-



lated and are prone to develop in children and adults before thirty-five years of age. The colors are varied and mixed. The consistency varies in different parts of the same growth from soft and mushy brainlike substance to firm elastic tissue. Cystic spaces with content of various kinds of fluid are found. Areas ranging from larger portions of organs to minute rudimentary organ structures are noted.

Microscopically, the tissues are largely fetal. It is characteristic for well-differentiated tissue to lie next to areas of wild growth of epithelial, endothelial, or sarcomatous pattern. One element of a teratoma may suppress the others.

Metastases occur most often in the abdomen but may appear in distant parts of the body. They may present a counterpart of the original tumor or as a carcinomatous or sarcomatous growth, a glial tumor, a chorioepithelioma, or a malignant tumor of undifferentiated growth.

The etiology is unknown. There are two theories: Marchand-Bonnet theory that isolated blastomeres are the source of these trigerminal growths, or that they arise from primitive unfertilized ova. It rarely occurs in women after the menopause, only five cases having been recorded. Only two teratoma were found in Kermanner's clinic among 1300 ovarian tumors over a period of thirty years.

Curtis presents a case occurring in a sixty-three-year-old woman, a Para. iv, whose father and a brother had died of carcinoma. The tumor measured 14 x 9 x 6 cm. He presents photomicrographs illustrating the variety of growth in different parts of the tumor.

**Theca Cell**—The writers, Banner and Dockerty,<sup>15</sup> reviewed 600 solid tumors of the ovary which occurred at the Mayo Clinic between the years of 1910 and 1940 inclusive. Blocks of tissue were

taken from each tumor and stained with H. and E., Sudan III, and a silver impregnation as a reticulum stain. In eight cases, some of the tissue was subjected to chemical analysis for its lipid fraction, and as control normal ovarian tissue was subjected to the same analysis. None of these tumors had been diagnosed as such before operation and so no urinary estrogen determinations were made.

The laboratory findings were then correlated with the clinical record as regards menstrual irregularities in the young and postmenopausal bleeding in older women.

The study of the available material showed them to be approximately 3 per cent of all of the solid ovarian tumors. The average age was fifty-nine years. Pregnancy had occurred at least once in 80 per cent. Symptoms were not constant in various cases. Sixty per cent had irregular vaginal bleeding. Of twelve patients over fifty-five, eight had postmenopausal spotting. In only one of the twenty-three cases was there postmenopausal bleeding with regular rhythm suggesting menstruation. Physical examination revealed a firm nontender ovarian tumor and frequent association with fibroids and one cervical and two fundus carcinomas were found. No breast hypertrophy was noted. The right side was involved two to one. The largest tumor was 12 cm. The average was 6 cm. in diameter.

The color varies from a brownish gray or pearly to a dull orange yellow. The consistency was firm but elastic. Degenerate central cysts may be seen in the larger tumors secondary to infarction and twisting of the pedicle of the tumor. No examples of Meigs' syndrome were found.

Histologically typical theca cells mixed with granulosa cell elements were seen

with the H. & E. stain. When silver impregnation methods were used, the reticulum fibrils stood out around the theca cells but not around the granulosa cells.

The opposite ovary was examined and no significant change was noted in twenty-one cases. The uteri seemed to have undergone myohypertrophy, which may be interpreted as estrogenic in nature and produced by the tumor in at least some of the cases. Carcinoma was observed in 22 per cent of the cases. Six cases had fibroids in the uterus.

Chemical analysis showed these tumors to be richer in cholesterol and cholesterol esters than normal ovarian tissue, but otherwise there was no striking difference.

Follow-up studies on twenty traced cases showed no malignancy from the ovarian tumor directly. Because of the inherent danger of carcinoma in the uterus, panhysterectomy is advised; but no follow-up x-ray or radium treatment is indicated except in those cases with a uterine carcinoma involving the cervix or fundus of the uterus.

### Cysts

**Bilateral Polycystic—Significance in Sterility**—Bilateral polycystic ovaries are associated with a definite clinical syndrome, the significance of which is not generally acknowledged by gynecologists. The characteristics of this syndrome are menstrual irregularity featuring amenorrhea, a history of sterility, masculine type of hirsutism, and, less consistently, retarded breast development and obesity. Extreme masculinization is sometimes noted in addition to hirsutism and there may be facial acne. Pelvic pain is not a consistent symptom but is one which occasionally causes the patient to present herself for examina-

tion. The ovaries are similarly and simultaneously enlarged but are difficult to palpate; therefore, pneumoroentgenography is of great value in establishing or corroborating the diagnosis. The cure of bilateral polycystic ovaries requires surgical treatment, with wedge-shaped resection of both ovaries.

In the past fifteen years, Stein<sup>16</sup> has been able to follow fifty-three patients upon whom a diagnosis of bilateral polycystic ovaries was made, corroborated by gynecography and treated by bilateral ovarian wedge resection. These patients consisted of twenty-three single women and thirty married women. In all, twenty-three of the single women, menstrual cycles were established postoperatively. Usually a normal monthly rhythm occurred and the secondary sexual characteristics were definitely influenced, favoring the feminine type. The original condition of bilateral polycystic ovaries did not recur in any case.

After bilateral wedge resection, all of the thirty married women had reestablishment of the menstrual cycle. There were thirty-one women (twenty eight from the married group and three from the single group who subsequently married), who were endeavoring to become pregnant. Twenty patients (64.5 per cent) became pregnant, resulting in twenty-six pregnancies and twenty eight babies. Periodic checkup postoperatively revealed that there were no recurrences of bilateral polycystic ovaries. Three single women who had febrile and painful postoperative courses developed a unilateral ovarian cyst with adhesions (5 per cent).

On the basis of this study, Stein recommends that bilateral polycystic ovaries associated with amenorrhea, sterility, and/or hirsutism be treated by bilateral ovarian wedge resection.

## CERVIX

### Cervicitis

**End Results in Treatment**—The pathology and clinical significance of cervicitis is well understood, but there remains to be developed a more uniform agreement on the choice of procedures to be applied in the management of the various phases of cervicitis. There is fairly universal acceptance of the therapeutic value of the cautery, but there still is much confusion as to the type of cautery best suited for the individual case. With this in mind, Finley<sup>17</sup> has in this presentation endeavored to determine the respective merits of the several methods of cauterization now in vogue. His observations are based on a series of 240 cases of chronic cervicitis, with or without erosion, cysts, eversion, or hypertrophy. All cervixes were biopsied both before and after cauterization, so as to determine the method most favorable to complete healing and freedom from ensuing complications.

The three accepted methods of cauterization, nasal tip, coagulation, and conization were used. Ninety-seven patients were treated with the nasal tip technic, fifty-two by coagulation, and fifty-seven by the conization technic. Comparisons were made as to the rate and type of healing following each therapeutic measure and as to resultant complications. The average rates of healing were found to be the same with all three methods. There was very little difference between coagulation and conization in the end histological picture. Fibrous tissue reaction was very low in both procedures, although slightly greater following cauterization. Complications most commonly encountered were hemorrhage, stenosis, and pyometra, and were most frequently seen following conization. Hemorrhage (six cases) usually occurred

from the tenth to the fifteenth day at the time of separation of the slough. Stenosis with resultant pyometra may be largely prevented by repeated dilation of the cervical canal. Findley found that internal menstrual tampons interfere with healing and he strongly condemns them. In all three groups, there was a high incidence of endocervicitis, 24 per cent of the nasal tip group, 12 per cent among the coagulation group; and 25 per cent in the conization group. This was due to the fact that the electrosurgical procedure was not carried high enough in the cervical canal to reach and destroy all of the infected cervical glands. All their methods of cauterization proved equally effective in the series investigated by Findley.

### Carcinoma

**Report of Second Survey**—Cashman<sup>18</sup> reports the results and conclusions of a second survey made of 10,000 cases of deep cauterization of the cervix in the Elizabeth Steel Magee and St. Francis Hospitals in Pittsburgh. The first survey was made in 1941 and covered a period of twenty-five years, which was completed in 1939. At that time there were two known cases of carcinoma of the cervix, one of which is still alive. The second survey was primarily to determine if deep cauterization of the cervix had succeeded in preventing cancer of the cervix. There were 4487 patients who were followed and no other case of carcinoma of the cervix was found. From the results of this survey Cashman concludes:

1. Chronic cervicitis seems to be a contributing factor in the causation of carcinoma of the cervix.

2. Cancer of the cervix is insidious in onset and, because of the late stages in which it is seen today, prevention of cervicitis, prevention of cancer by

adequate treatment of existing cervicitis, and early diagnosis by periodic examination of women over twenty-five years of age, offer the best solution of the problem.

3. In order to destroy infection in the cervix by cauterization, it is often necessary to cauterize deeply and extensively.

4. Careful postoperative care and treatment are necessary to prevent stenosis of the cervical canal after deep cauterization when the uterus is not removed.

5. As far as known, deep cauterization of the cervix has been an effective method of preventing cancer in this series of 10,000 cases, for only 2 cases of cancer of the cervix are known to have occurred in this series.

**Treatment—*Pelvic Lymphadenectomy***—Metastases in the regional lymph nodes have long constituted a stumbling block in the treatment of cervical cancer. In many instances, glandular involvement occurs only in association with extensive local growth, making a combination which spells doom for the patient. In other instances, regional node metastases exist even when the local growth is early enough to permit surgical eradication or destruction by radiation. It is in the latter group that Morton<sup>19</sup> is interested, for in them there exists at least the possibility of removing or destroying all the involved tissues. With the administration of high voltage roentgen therapy, the possibility of destroying cancer in the parametria and in the regional glands moved to the fore. However, there still remained a group of cases in which local cervical response to radiation promised much, yet death occurred soon after, presumably because of the survival of cancer in the regional nodes. This consideration led Taussig to suggest a surgical resection of the regional lymph nodes as

a supplement to radiation in the early inoperable group of cases. In 1935, Morton and his group at the University of California Hospital started to perform this operation upon certain selected patients.

Of great importance in deciding the indication of such a procedure as lymphadenectomy is a knowledge of the incidence of glandular involvement, particularly in relation to the degree of advancement of the local growth. Most observers have reported an incidence of approximately 50 per cent glandular involvement in cases in which parametrial invasion was confirmed by microscopic sections on material obtained at radical operations. It has been shown by many that gross enlargement of glands did not necessarily mean metastatic involvement. Conversely, unenlarged glands have been found involved by cancer. Finally, it has been observed that glandular metastases sometimes occurred even when the local cervical growth still remained clinically confined to the cervix, although the glands occasionally remained free even after considerable parametrial spread, a fact which must account for the cures which were obtained by surgery in cases with a rather extensive growth.

Morton selected cases for operation only those in which the immediate local response to radiation was good, whereas Taussig performed his operations more routinely, and before he had an opportunity to study the local reaction. The author's feeling has been that it was useless to resect the regional glands if there was not a reasonable chance of a successful outcome so far as the cervix proper was concerned.

In all, a total of sixty five cases had lymphadenectomy performed. In thirty-five cases, the patients received courses of high voltage x-radiation in addition to approximately 4500 mg. hr. of *radium*

distributed in and about the cervix before operation. The dose of *roentgen therapy* varied between 2000 and 4000 r. to each of four fields, two anterior and two posterior. In twenty-eight instances, *radium* only was used in small doses as preparation for the radical operation.

The operation employed involves a laparotomy approach, the exposure of the depths of the broad ligaments and the lateral walls of the pelvis, after removal of the tubes and ovaries, and resection of the gland-bearing areolar tissues lying in the bifurcations of the common iliac arteries and in the obturator fossae. The areolar tissue about the uterine arteries and the ureters, as well as that lying about the iliac veins just before their exit beneath Poupart's ligaments, has also been removed when glands could be palpated in these structures. The operations have not been difficult though occasionally they have been complicated by troublesome hemorrhage from the plexus of uterine veins. In two cases in which the Wertheim operation was performed in addition to lymphadenectomy, death from cellulitis and generalized pelvic infection followed within a period of two months; no cancer remained at autopsy. There has been no mortality from the operation of simple lymphadenectomy alone. Obesity and old age have been considered contraindications.

The actual five-year results in this group of cases are of little significance in evaluating this procedure as a method of treatment. It is of interest that the lives of at least three women, from whom glands involved by cancer were removed, were apparently saved by this procedure. Of the ten patients in the five-year group in whom glands were involved, only three survived, while of eighteen

patients in whom glandular involvement was not found, sixteen survived the five-year period. While these figures seem to point a very ominous finger at glandular involvement, at least five of the nine deaths were due to the local cervical recurrence and invasion of cancer, and not to the existence of cancer in the glands.

If the premise upon which Taussig based his operation, namely, that metastases in lymph nodes are peculiarly resistant to radiation, can be substantiated, then his procedure deserves a much more extended trial. If, however, it can be shown that modern x-radiation may actually destroy metastatic cancer in lymph nodes, then this nonoperative and possibly more comprehensive method may prove superior. The number of cases so far subjected to operation is too small to determine definitely its sphere of usefulness in the treatment of cervical cancer.

*Interstitial Radium Needles* (Rhode Island Hospital)—*Supplemental Report*—Waterman and DiLeone<sup>20</sup> report and review ten-year survival rates on 309 cases of carcinoma of the cervix treated by *interstitial radium needles* from 1926 to 1933, which had been previously reported for five-year survivals; on a second series of 198 cases treated between 1934 and 1938, and a review of the total of 507 cases from 1926 to 1938. Of the 309 cases previously reported as to five-year survivals, 100 survived five years and 69 survived ten years or 69 per cent of the five-year survivals. Of the 198 cases in the new series, there were 66, or 33 per cent, five-year survivals.

The complications due to radium treatment showed a 7.9 per cent incidence of vesicovaginal fistula in the whole series of 480 cases treated. In

the last 177 cases, 15, or 8.4 per cent, developed fistula. No Stage I case developed fistula. There were 5 cases in Stage II, 8 cases in Stage III, and 2 cases in Stage IV developing fistula after treatment. In addition, 11 cases developed urinary tract lesions other than fistula. Thus, out of 177 cases treated, 11.8 per cent developed urinary tract lesions as a result of treatment.

The following intestinal complications were noted: (1) Ten cases of bleeding and tenesmus; (2) one large rectal ulceration thought mistakenly to be cancer and resected; (3) one case of necrosis of the transverse colon with perforation which was repaired followed by recovery of patient; (4) one case of ulceration and perforation of the rectosigmoid into the peritoneum with peritonitis resulting in death; (5) one case of intestinal obstruction which occurred about one year after treatment for cancer of the cervix complicated by a large fibroid.

The younger age group of patients, that is, under thirty, had a larger five-year survival incidence than the older age group. Statistical analysis suggests that this was due to the fact that the younger age group came in for treatment sooner, and with less involvement, and consequently had a better prognosis.

Waterman and DiLeone individualize upon the dosage used refraining from a single pattern. They attempt to place the needles about the growth, depending upon the direction in which the tumor is found extending; thus, from six needles in small lesions to sixteen in larger lesions were used in this series. In the Stage II and Stage III groups, the dosage varied from 1000 to 10,000 mg. hours. In the Stage II series, the best five-year survival rates occurred in a group of forty-one cases which received

between 5000 to 7000 mg. hours, while in the Group III cases between 4000 and 6000 mg. hours offered the best results.

**Wertheim Operation**—The arguments for the treatment of carcinoma of the cervix by surgical means bears repetition: (1) If the cervix has been removed, no cervical cancer can regrow in it as a recurrence; (2) certain cancers of the cervix are radiation resistant, a fact proved at the Pondville Hospital, where multiple biopsies are performed at the time x-ray and radium treatments are being carried out; (3) there will be less damage to the bowel if surgery is undertaken. Lately, forty six cases of serious bowel injury have been found in the author's clinics. (4) From the work of both Bonney and Taussig, it is obvious that patients with lymph node metastases can be cured by surgery in some instances, and Meigs<sup>21</sup> believes that it is not possible to cure with radiation cancer in lymph nodes deep in the pelvis; (5) the study of vaginal smears presents a new and sixth reason for advocating radical surgery since after the Wertheim operation these smears are negative, while, after four or five years following radiation, vaginal smears occasionally show cells that suggest a recurrence or a persistence of carcinoma.

The total series of cases operated upon is sixty-five or about 15 per cent of the total number of patients seen with cervical carcinoma. The patients selected for surgery should be young, preferably under fifty years of age, and in good physical condition. It is important that they are thin; obese women should not be chosen. The tumor may involve the cervix in part or entirely; it may advance upon the vaginal wall to not over 1 cm. from the cervix. The cervix should be movable on vaginal or rectal examination. Palpation of lymph nodes in the

iliac, ureteral, or obturator regions is no excuse for not operating if the other reasons for selection are satisfactory. It is exactly this type of patient that Meigs hopes to be cured by radical surgery. If pyelography demonstrates that the ureter is dilated but the lesion seems operable, the patient should be given the benefit of the doubt, for surgery may cure such a patient if the block in the ureter is due to pressure of a node.

The operation performed by Meigs he prefers to call the Wertheim-Clark plus the Taussig operation. The pelvic lymph node dissection being that advocated by Taussig. The operation includes the complete dissection of the pelvic lymph nodes from the bifurcation of the aorta down, plus the removal of the cervix, vagina, and parametrium. The only real and serious complication is damage to the ureter and consequent ureterovaginal fistula. Eight or 12.3 per cent of the sixty-five patients in the group developed ureteral fistulas. With increased knowledge of the blood supply of the ureter, it is hoped this obstacle of the operation can be overcome.

Twelve patients or 18.4 per cent had lymph node involvement and all of them would have died if radium were the treatment of choice. In this group of twelve patients, follow-up revealed that 41.6 per cent could not be considered as cured as they are dead or have had recurrences. Fifty-eight and four-tenths per cent are known to be living and well. There is no proof that preoperative radiation was beneficial in the twenty-four patients so treated. From the surgical technical point of view, there was very little difference in the dissection during the operation. In the entire group of sixty-five cases, there were no postoperative deaths, an indication of the safety of the operation in skilled surgical hands.

## UTERUS

### Cervix Uteri

**Carcinoma—Interval Report on Treatment, Results, and Complications**—This report is based on a series of 1111 cases of carcinoma of the cervix treated at the Free Hospital for Women from 1902 to 1938. The percentage of women who were alive five years after first treatment is as follows: 1902 to 1913, 12 per cent; 1914 to 1918, 19 per cent; 1919 to 1923, 23 per cent; 1924 to 1928, 28 per cent; 1929 to 1933, 38 per cent, and 1934 to 1938, 43 per cent. Seventy-one per cent of the patients alive after five years were alive after ten years, and 75 per cent of those alive after ten years were alive after fifteen years.

Radium was first used late in 1916. Complications from treatment occurred in five patients in the period 1916 to 1918; one incisional hernia, one vesicovaginal fistula of surgical origin, and one from radium. Two patients developed both vesicovaginal and rectovaginal fistula from radium.

The period from 1924 to 1928 showed an improvement in results. This is attributed to the giving of single doses, 200 or 225 mg., of radium, screened with 0.5 mm. of silver and 0.5 or 1.0 mm. of brass for twenty-four to thirty hours, 6000 mg. hr. being the maximum dose.

During the period 1929 to 1933, three changes in treatment were introduced. The first was begun in 1930 and consisted of administering radium in two doses of 2000 to 3600 mg. hr. each, within ten days of one another for a total of 4800 to 6000 mg. hr. In 1931, the second change was made. Radium applicators of 1.0 mm. brass with additional screening of 1.0 mm. lead were much more frequently used. The third change was the administration of 1600 r. with a 200-kv. apparatus immediately

after the first application and repeated after two months. A gratifying improvement in results ensued in spite of a distressing number of deaths and complications attributable to treatment. During the period 1934 to 1938 there was no change in radium treatment. Two well-screened doses of 2000 to 3000 mg. hr. were most often employed. The total dose of x-radiation did not exceed 4800 r. and much more often was 3200 r. or less because of a fear of complications.

Fifty-eight patients, 5.2 per cent of the 1111 cases, had a supravaginal hysterectomy performed prior to the diagnosis of cervical cancer. Furthermore, fifteen patients had previous bilateral oophorectomy and eight had bilateral salpingo-oophorectomy. Five more had bilateral salpingectomy and two had both tubes ligated. Thus, thirty patients, 2.7 per cent of the series, developed cancer in the cervix of the uterus that had been rendered a completely useless organ or one capable only of menstruation.

Deaths and complications from radiation were due primarily to overtreatment. Smith and Dresser<sup>22</sup> consider anything over 5400 mg. hr. given in one application and anything over 6000 mg. hr. given in two applications as an overdose of radium. The maximum safe amount of 200-kv. x-radiation when combined with the above dose of radium is 6000 r. It is better to give all radiation within six weeks and to administer x-ray therapy first except in cases with hemorrhage. Retreatment is only occasionally beneficial and at that only for local vaginal recurrences. It is safer to withhold additional therapy unless the evidence for recurrence is convincing.

In a comparison with surgical treatment, the authors are convinced that the radical operation should be resorted to only in cases of operable radio-resistant cancers.

**Squamous Metaplasia** - Following a brief review of the conflicting ideas concerning metaplasia in regard to its precancerous nature and the origin of the cells, Auerbach and Pund<sup>23</sup> emphasize two points they have found to be of value in the differential diagnosis. First, the position and morphology of the cells which have been aptly described, especially as regards the outward displacement of the mucous-secreting columnar cells; second, the "festooning" effect which is achieved by the squamous cells in growing over the microscopic undulations of the cervix. This survey is based on 100 consecutive cervixes, of a group of over 600, in which a maximum of satisfactory sections were obtained.

Squamous metaplasia was observed in 72 of the 100 cervixes obtained varying from minimal to maximal, the latter representing almost complete transformation of the columnar epithelium of the lower cervical canal. Race appears to have no effect on the incidence. The youngest in the series was twenty one and the oldest fifty one. There is a significant increase in incidence from the third through the fifth decades, and this rise is emphasized by a correlated rise in severity. There is no correlation between parity and the presence of metaplasia. The menstrual history and the endometrial phase were noncontributory. Gross appraisal of laceration and eversion was made on the fresh specimen and these were without effect as factors. Inflammation was difficult to appraise, as inflammation with metaplasia was observed in thirty instances; metaplasia without inflammation was observed in forty-two cases and neither metaplasia nor inflammation were seen in nineteen cases.

Fibromyomas constituted the most common cause for hysterectomy in this series and occurred in a total of fifty-



seven cases, alone in thirty-seven, and in combination with salpingitis in twenty. Of these fifty-seven cases, thirty-six, or 81 per cent, had metaplasia, but salpingitis had no effect. Malpositions showed no influence on the incidence, but three cases of frank prolapse were all positive.

Preinvasive carcinoma occurred twice in this series. In both cases, there was metaplasia in addition to the frank neoplasia, but the two processes were entirely distinct.

The individual factors which appear to exert an influence on the development of metaplasia are age of the patient and inflammation or irritation of the cervix. The rising curve of incidence of squamous metaplasia from the third through the fifth decades of life roughly parallels the curve of declining ovarian activity with relative hyperestrinism.

Auerbach and Pund are of the opinion that chronic inflammation plays a more important part in the process than the figures indicate, although its mechanism as a local stimulus is vague. The presence of metaplasia in chronic inflammatory disease seems removed from any function in the healing of erosions, as the ratio in everted and noneverted cervixes is almost exact (72 per cent and 73 per cent), and eight or nine nulliparous cervixes grossly free from any lesion showed varying degrees of metaplasia in the endocervix. Circumferential involvement of the endocervix just proximal to the external os was a fairly frequent observation in nulliparous specimens and in parous specimens in which near perfect healing produced some degree of stenosis. The dilated canal immediately above was usually filled with mucus, suggesting that the secretion itself may be sufficient stimulus to induce basal cell proliferation with squamous metaplasia.

Nothing was observed to suggest direct conversion of metaplastic to neoplastic cells. However, the tendency of cancer cells to grow along natural surfaces, displacing the preexisting epithelium, whether columnar or squamous, and to remain *in situ* for some time suggests a kinship to the metaplastic cells.

### Prolapse

**Surgical Treatment** — There has been a trend during the past two decades toward correcting prolapse of the uterus by the vaginal route unless intrapelvic disease necessitates laparotomy. TeLinde<sup>24</sup> is of the opinion that one should not approach the subject with a fixed plan of operation. Each case should be judged and treated as an individual problem. In selecting the best operative procedure in an individual case, several factors must be taken into consideration. The most important of these factors are: The general physical condition of the patient; the desirability of preserving menstruation; the desirability of preserving the child-bearing function; the degree of descensus; the condition of the cervix and corpus uteri; the presence of, and degree of, cystocele; the presence of, and degree of, rectocele or enterocele.

In discussing the cure of prolapse of the uterus, it is advisable to consider the supporting structures which have failed to hold the uterus in correct position and how best to utilize these supporting structures in restoring the uterus to its normal position, or in supporting that portion of the uterus which is permitted to be retained and/or the vagina. The structures which are concerned in maintaining the uterus in normal position are: The round ligaments; the uterosacral ligaments; the base of the broad ligaments (cardinal ligaments,

etc.); the fascia lying between the anterior vaginal wall and the vagina; the fascia lying between the posterior vaginal wall and the rectum, and the floor of the pelvis (the pubococcygeal fibers of the levator ani muscles). Some or all of these structures are utilized in the various operations designed to restore support to the pelvic structures.

Young women suffering from various degrees of prolapse associated with the allied conditions of cystocele, relaxed vaginal outlet and rectocele frequently desire more children. Their wishes must be respected and often a pessary can be used to advantage as a temporary expedient. TeLinde is of the opinion that, if possible, surgery should be deferred in this group of patients for two reasons: first, radical plastic vaginal repairs will suffer injury at subsequent deliveries; second, the best types of operation for prolapse are not compatible with future pregnancy. If surgery is essential during the child-bearing period, the author prefers a modification of the Gilliam suspension, often combining it with shortening of the uterosacral ligaments and/or advancement of the bladder peritoneum onto the uterus.

There is another group of relatively young parous women who present themselves with various degrees of descensus associated with relaxed outlet, rectocele, and cystocele. These women have as many children as they desire and would often welcome sterilization. When the descensus is of first degree, a Manchester operation with sterilization is a quite satisfactory procedure. In young women and in those over forty with more severe prolapse, TeLinde prefers the Spalding-Richardson composite operation. The operation is a prolonged one and should not be done if the physical condition of the patient is such as to make an extensive operation ill advised. In those cases,

the Watkins' interposition transposition operation is quite satisfactory if the uterus is healthy and of proper size.

When prolapse and its allied conditions exist with benign uterine disease, vaginal hysterectomy is, in most instances, the operation of choice. However, since the benign uterine disease is situated in the portion of the uterus amputated, the Spalding-Richardson operation is preferred, because the results in supporting the vagina have been better than in vaginal hysterectomy. There is still another group of patients in which gross intrapelvic disease exists and in these combined laparotomy and plastic operation must be the procedure of choice. TeLinde prefers the Lefort colpocleisis in elderly women who are poor surgical risks.

The technic of the Spalding Richardson operation is presented in detail because it is generally unknown. An inverted T-shaped incision is made in the vagina as in the first step of the cystocele operation, and the bladder dissected from its attachment to the cervix. The pubovesicocervical fascia is then dissected from each flap. The cervix is next amputated. The author then covers the posterior lip of the shortened cervix with a flap of mucosa that has been dissected free and then drawn into the canal with a mattress suture. The cervical amputation is much less bloody if the cervical branches of the uterine vessels are first ligated bilaterally. The vesicouterine pouch of peritoneum is then incised and the fundus of the uterus delivered by means of traction sutures or tenacula. After clamping the uterine end of the round ligament tube and ovarian ligaments, a supravaginal amputation of the corpus at the desired level is performed. The stump is then closed and the round ligaments, tube, and ovarian ligaments are sutured into it. The uterosacral and bases of the broad ligaments are attached

to the remaining segment of the uterus, and are utilized in building up support of the vagina. The edge of the vesico-uterine peritoneum is then sutured to this remaining portion of the uterus. The pubovesicocervical fascia is then brought together in the midline by interrupted sutures beginning beneath the urethra, continuing beneath the base of the bladder and finally covering the stump of the uterus. The anterior lip of the cervix is then covered over with vaginal mucosa, flaps of which have been trimmed to the proper size. The pelvic floor and rectocele are then repaired.

In the private service of Richardson and of TeLinde and in the public ward service of the Johns Hopkins Hospital, the operation has been performed on approximately 100 women with satisfactory results. TeLinde is of the opinion that the Spalding-Richardson operation meets the desired objective of an operation for uterine prolapse when further pregnancies are not desired. The diseased portion of the cervix is removed, thus removing a source of leukorrhea and a potential site of neoplasm. The corpus uteri is removed and with it the danger of endometrial cancer as well as fibroids. The bases of the broad ligaments and the uterosacral ligaments have not been crushed as in vaginal hysterectomy and are preserved for support of the vagina. Follow-up study reveals that the vagina is well suspended and is of normal depth and caliber.

**Vaginal Hysterectomy**—The two procedures employed almost to the exclusion of all others in the treatment of descensus of the uterus are the Manchester operation or one of its modifications; and vaginal hysterectomy, together with the use of the cardinal ligaments, the pubocervical fascia, the uterosacral ligaments, and the upper portions of the broad ligaments for the

construction of a supporting structure which will uphold the vaginal vault and the bladder. The intelligent treatment of uterine descensus requires a clear conception of the mechanics of uterine support and of the anatomy of the structures by which this is accomplished.

Danforth<sup>25</sup> has treated the greater part of his cases by vaginal hysterectomy. In a little more than 600 vaginal hysterectomies, the operation was done for descensus of greater or less degree in 160 cases.

In so far as the technic is concerned, there were two groups of cases. In those where the uterus was entirely out, or at least a large part of its bulk escaped from the vagina, Danforth used the Mayo operation which had been well described by Ward with modification. In addition to that method described by Ward, the use of the pubocervical fascia, dissected free in the early part of the operation and brought together over the united broad ligaments, is a valuable part of the procedure and materially adds to support. An inverted T-shaped incision is made on the anterior wall extending nearly to the urethra. Flaps are freed on each side and the fascial layer is dissected free. The anterior peritoneal fold is then opened. The incision is extended behind the cervix and the posterior peritoneal pouch is opened. The uterosacral ligaments are divided, the uterus turned anteriorly and the broad ligaments caught in three clamps on either side and the uterus removed. The next step is to approximate the uterosacral ligaments. In patients in whom there is a marked enterocele, it adds to the efficiency of the operation to resect a portion of the uterosacral pouch. An efficient closure of the posterior part of the weakened uterine supports is a very important part of the operation, and Danforth feels that 'here is a frequent



curved forceps introduced into the internal ring behind the fascia and above the muscle grasps the round ligament and pulls it through the ring backward over the rectus muscle and held by Allis forceps. The left round ligament is treated in the same manner.

2. Both round ligament loops are drawn mesially along the lower aponeurotic leaf until the uterus is brought into the desired position.

3. The peritoneum is closed and the recti muscles approximated. The round ligament loops are then sutured to the posterior surface of the aponeurotic leaf with mattress sutures. The aponeurosis is then closed with a running suture which should include but not surround the ligaments below.

The authors state that the operation is safe and is associated with the minimum of trauma. It is safe for future childbearing, if this is contemplated. Several of their patients went through normal labor and delivery. They advocate this incision for suspension operations of the uterus and other gynecological procedures. They claim for this method less pain than when the ligaments are brought through the aponeurosis and left subcutaneous.

### Dysmenorrhea

**Spasmodic Dysmenorrhea—Hypoplasia of Uterus.**—The pain of spasmodic dysmenorrhea is related to contractions of the uterus. The difference between painful and painless contractions lies in their character rather than their strength. The particular pattern of uterine motility causing pain during menstruation is unknown, but the view which supposes inco-ordination of different areas of the uterus, or disturbed polarity of the uterus, has still to be disproved. The theory which supposes uterine hypoplasia as the cause of the abnormal uter-

ine contractions and the evidence on which it is based are critically examined by Jeffcoate and Lerer<sup>27</sup> in the light of what is known about the development of the uterus.

An analysis of the histories of 829 patients suffering from spasmodic dysmenorrhea shows (a) not more than 27 patients had definite signs of uterine hypoplasia; (b) the age of the menarche was usually within normal limits; (c) scanty and infrequent menstruation was the exception and most women had a regular cycle; (d) endometrial studies in 111 cases showed, with 2 exceptions, that the histological phase agreed with the time in the menstrual cycle. Painful menstruation is usually ovular in type; (e) 457 patients had some minor malformation or malposition of the uterus, but these faults are not accepted as an indication of hypoplasia; (f) the existence of an interval between the menarche and the onset of dysmenorrhea in a large percentage of cases is confirmed. This in itself is evidence against the hypoplasia theory. An analysis of a second series of eighty-six patients, all of whom had a hypoplastic or atrophic uterus, shows that of the twenty-eight women who were menstruating only one had dysmenorrhea of an incapacitating degree.

The effect of *estrogen* on a hypoplastic uterus depends on the ability of the organ to respond. If the uterus is insensitive, then *estrogen therapy* is useless. If, however, the uterus is sensitive, then there is no point in increasing its size temporarily unless the cause (usually ovarian underactivity) is connected. Furthermore, if the cause is successfully treated, the hypoplasia is automatically cured and *estrogen* is unnecessary. The value of *estrogen therapy* in *spasmodic dysmenorrhea* is open to question. If it does give relief, even tempo-

rary, then it does not necessarily do so by overcoming hypoplasia.

Jeffcoate and Lerer are of the opinion that the evidence at hand is insufficient to prove or disprove the hypoplasia theory of dysmenorrhea and it will remain so as long as the pathology of uterine hypoplasia is in doubt and its diagnosis depends on the opinion of individual clinicians.

**Primary Dysmenorrhea — Treatment with Deproteinized Pancreatic Extract (*Depropanex*)**—Grossmann,<sup>28</sup> after reviewing the literature, is unable to find a therapeutic agent available to the clinician that will afford consistently favorable results in the treatment of dysmenorrhea. It has been shown that dysmenorrhea occurs only in the presence of active uterine contractions, and that these contractions are spastic in character. The effect of a nontoxic, spasmolytic agent, *depropanex*, which is a deproteinized pancreatic extract, was studied when administered to two groups of patients. The first group of twenty-five patients encountered in private practice offered uniformly consistent and favorable results. These patients received sixty-three treatments, consisting of from 1.5 cc. to 4 cc. of *depropanex* intramuscularly. Complete relief from dysmenorrhea was afforded within from fifteen minutes to one hour subsequent to administration of fifty treatments. Partial relief was afforded within the same period of time after eleven treatments.

Thirty-one patients in the second group (industrial practice) received forty-one treatments, twenty-two, or 53.7 per cent, of which afforded complete relief, and six, or 14.6 per cent, afforded partial relief. Favorable response was denied after thirteen treatments (31.7 per cent). The striking disparity of results obtained in the two

groups is accounted for by the fact that among the industrial group of patients some were accustomed to oral medication and, in many instances, fully expecting to be excused from work, resisted parenteral treatment. Because of the large labor turnover in the industrial plants, it was frequently impossible to do follow-up studies or to repeat the medication in larger doses.

**Functional Dysmenorrhea — Treatment with Pregneninolone**—Harding<sup>29</sup> treated eighty-two patients afflicted with functional dysmenorrhea by oral administration of 5 mg. tablets of *pregneninolone* daily. All patients were treated in the premenstrual phase. There was 50 per cent or more improvement in sixty patients and less than 50 per cent improvement in twenty-two patients. Six patients were classified as worse because there was more pain during the months treated. This percentage was based on the amount of pain estimated by the patient and her relatives, the request for pain relieving therapy and the amount required, the length of time the patient was bedridden or unable to work, her general appearance, etc.

The prevention of pain was considered temporary as the patients were usually only benefited in the month that medication was taken.

Before treatment, menstruation was essentially regular in thirty-nine patients and irregular in forty-one patients. In this series there was a tendency for earlier menstruation to occur except when menstruation was quite early before treatment. Where early menstruation had been caused in previous months by the tablets, starting the use of *pregneninolone* later in the cycle prevented the onset of menstruation before the twenty-eighth day.

Twenty additional patients were given injections of *progesterone* in doses of

5 mg. to 15 mg. during the time that the patient complained of severe pain. The results of this treatment were disappointing, and as very little relief was obtained, this method was discontinued. Later, twenty-two patients were given *progesterone* injections between menstrual periods. The results were not as satisfactory as were obtained with the oral use of *pregneninolone* and were discontinued because they caused too much inconvenience and were too expensive for a treatment usually giving only temporary relief. The oral administration of *pregneninolone* has many advantages, such as simplicity, harmlessness, low cost, and timesaving to both the patient and physician.

**Essential Dysmenorrhea — Treatment with Pavatrine**—Medical science is still ignorant as to the true cause of dysmenorrhea in the absence of pelvic pathology, and as dysmenorrhea is a symptom and not a disease, no one routine of treatment regularly gives any measure of success. For the most part, also, it is usually not possible to differentiate in any one individual the type of dysmenorrhea present, and there is always overlapping of the classified types: (a) The neurotic; (b) the obstructive; (c) the hypoplastic, and (d) the constitutional.

In the series of Weinberg's<sup>30</sup> 141 cases have been reviewed. Forty-one of these could be explained on the basis of pathology that required operative correction or treatment, and are not included in the series. The rationale of therapy in the functional cases was based on the fact that the pain is certainly related to the uterine musculature or its innervation or both. *Pavatrine* possesses both musculotropic and neurotropic action. Its action simulates that of morphine, but it has the advantage of being nonnarcotic. Its antispasmodic

property has been demonstrated by Bickers.

Each patient was given a prescription for *pavatrine* and instructed to take one tablet three times a day after meals, beginning three days before the onset of the expected period and likewise on the first day of the period. Each patient was also given a second prescription for capsules, each containing *phenobarbital*, 0.3 gm. ( $\frac{1}{2}$  grain); extract *hyoscyamus*, 0.05 gm. ( $\frac{5}{8}$  grain), and *amidopyrine*, 3.0 gm. (5 grains). She was told that this was an "emergency" drug and was instructed not to use it unless her cramps were painful and to take one capsule every four hours as long as she was uncomfortable. In this way an estimate of the amount of relief obtained by *pavatrine* alone could be made, for if it was not necessary to take any of the capsules, the results were considered excellent. If, however, three or more capsules were necessary in any twenty-four hours, then obviously the *pavatrine* was of no measurable value; thus, in forty-eight cases there was complete relief; in nineteen cases, one capsule was occasionally necessary; in twenty-three cases, two capsules were necessary, and ten cases were total failures, three or more capsules being required. No case is recorded which had not been treated for at least six menstrual periods and, as a further check, one half the cases which responded well to *pavatrine* were asked to omit it for one month. In this latter group, there was a return of the dysmenorrhea in every case. Three of the cases were failures because of an apparent idiosyncrasy of the drug. This consisted of a severe trembling of the hands and a complete feeling of inability to control locomotion. This sensation is unquestionably due to the marked relaxing effect

of the drug and in such patients it should be discontinued.

**Exercises**—Haman<sup>31</sup> treated a group of 129 patients with dysmenorrhea with special exercises. Eighty-four of these patients suffered from primary and forty-five from secondary dysmenorrhea. All patients treated had a severe type of dysmenorrhea being forced to bed during the menstrual period.

The exercises are very simple to perform; they take less than five minutes a day, and require a minimum of space; they may be done at home, and need be carried out usually for only two or three months before improvement results. There are three positions. *Position 1*—The patient stands at right angles to a wall at such a distance as will enable her to comfortably rest her left elbow on the wall on a level with her shoulder. The pelvis is tilted forward and, while in this position, the patient touches the wall with her hips, keeping her knees straight. Care must be taken not to twist the body or allow the elbow to slide up or down along the wall. *Position 2*—The same procedure is repeated, using the right elbow. *Position 3*—The patient faces the wall against which she rests both elbows. The pelvis is tilted and the patient stretches until her pelvis touches the wall. The heels remain on the floor and the knees are kept straight (the positions are well illustrated). Each position is assumed three times and repeated three times per day.

Eighty-four and five-tenths per cent of all patients suffering from severe dysmenorrhea experienced definite relief on this exercise regimen. In many instances, the beneficial relief lasted for at least twenty months, which was the limit of the follow-up period in this investigation. Within the subgroup of those afflicted with primary dysmenorrhea, the percentage of alleviation was 89.3 per cent.

## Abdominal Hysterectomy

**Observations Based on a Series of 1925 Patients** The policy of hysterectomy, subtotal or total, has varied since 1926 at the gynecology clinic of the University of Iowa. Since 1938 more than 90 per cent, and since 1940 more than 95 per cent of all abdominal hysterectomies have included the cervix. Of a total of 2820 operations, 1925 were total hysterectomies. Five senior staff members performed 36 per cent, eighteen senior residents with assistance usually of lower ranks performed 39 per cent and assistant or associate residents, generally assisted by more experienced operators, performed 25 per cent of the operations. The mortality rates were 2.9, 2.0, and 0.6 per cent, respectively.

The only variation of the usual techniques that Mengert and Stoltz<sup>32</sup> mention is that the vaginal apex was left open more often than closed, and that no attempt was made in any way to support the vagina with the round, ovarian, or infundibulopelvic ligaments.

The principal indications for operation were fibromyoma of the uterus, 856 cases; functional bleeding, 372 cases; pelvic inflammatory diseases, 329 cases; benign ovarian tumors, 318 cases; malignant uterine tumors, 167 cases; malignant ovarian tumors, 67 cases, and miscellaneous diagnoses, 215 cases.

Complications, usually of a technical nature, were experienced in 1013, 53 per cent of the patients listed, and by and large were relatively minor. Twenty-three of the thirty-eight fatalities occurred in the group of patients with complications, although the chief complicating factors were adhesions and bleeding; principal concern was associated with large bowel, ureteral and bladder injuries which occurred twelve, ten, and twelve times, respectively. The



author's comparative experience reveals that bowel and bladder injury occurs with similar frequency in any type of abdominal hysterectomy. On the other hand, ureteral injury occurs more frequently in total hysterectomy. Ureters were injured in ten women, with nine repairs, at the time of initial operation. Subsequent operation for reimplantation was necessary in one patient. Morbidity rates were similar to those for any hysterectomy series, irrespective of the type of operation. Infection of same type, chiefly peritonitis, accounted for twenty-two of the thirty-eight fatalities.

**Impressions Based on 135 Cases—**Supravaginal hysterectomy has been a standard gynecologic procedure for many years, and has been very successful in the cure of symptoms produced by such lesions as myomata uteri, adenomyosis uteri, functional uterine bleeding, partial descensus of the uterus, pelvic inflammatory disease, endometriosis, endometrial polyps, and benign uterine adnexal disease. In all of these conditions, it was thought advantageous or not disadvantageous to conserve the cervix uteri. Some of the advantages which are attributed to supravaginal hysterectomy have been the simplicity of technic, slight blood loss, absence of postoperative morbidity, and very low mortality. Besides these immediate advantages, great importance has been ascribed to the cervix uteri as a fundamental structure in the human female. Physiologic observations and knowledge accumulated in the last two decades have allowed for tremendous extensions of surgical procedures, and what was considered adequate and successful surgery twenty years ago does not apply today. The fact that complete hysterectomy is a more difficult and dangerous operation to accomplish without adequate experience has no right to influence our judgment as to its merits.

It is up to the gynecologist to train himself to overcome the technical difficulties and do the operation that is to the patient's ultimate advantage.

The authors'<sup>33</sup> technic is an extension of the technic ordinarily used for supravaginal hysterectomy. A self-retaining catheter is inserted into the bladder preoperatively and left in for seventy-two hours postoperatively. After mobilizing the uterus and adnexa, the corpus is grasped with a large tenaculum except in cases of malignancy or pyometria. The round ligaments are ligated and separated from the uterus, and the bladder peritoneal flap is developed and separated from the uterus for a short distance. The ovarian vessels are ligated and separated from the uterus. The broad ligaments are separated from the side of the uterus to the position of the internal os of the cervix. The uterine vessels are exposed, ligated, and cut above the ligature and then the vessels are dissected from the side of the uterus. The fascia which lies over the cervix is then separated from the cervix and the bladder is separated from the vagina as far as necessary. After partial separation of the uterine vessels on both sides, the uterosacral ligaments are exposed and ligated and separated from the uterus at which time mobilization is complete. After complete control of the circulation to the uterus, the whole structure is separated from the vagina with a knife cutting perpendicular to the axis of the vagina. The vaginal canal is closed with a continuous suture of fine catgut placed very lightly and in such a way that the vaginal mucosa is inverted into the canal. The round ligaments, infundibulopelvic ligaments, the perivaginal fascia, and the uterosacral ligaments are fixed to the vault of the vagina. All raw surfaces are covered with peritoneum. The authors prefer to use No. 0 or smaller

catgut sutures throughout the procedure. The anesthesia used for most of these cases has been continuous or fractional spinal with special consideration for small doses.

In the series of 132 cases, there was no immediate mortality. Fifty-two cases were morbid, 23 of which had a post-operative reaction for which there was no explanation. There were 12 cases of urinary tract infection, 4 wound infections, 1 pyelitis and retained sponge in vagina, 1 case of thrombophlebitis, and 1 case of perirectal abscess.

The chief indication for total hysterectomy is usually cited as the removal of a possible carcinomatous site. Not enough emphasis has been made of the retained cervical stump as a cause for minor gynecologic disturbance to indicate its removal.

In the follow-up of these cases, there were granulations in the vaginal vault in twenty-seven patients. Vaginal shortening occurred in one patient, but in many the impression obtained was that the vault was actually lengthened. After studying many vaginal smears, Mohler and Bishop are of the opinion that normal vaginal biology exists after complete hysterectomy and that the climacteric occurs at its normally expected time when the ovaries have been conserved.

**"Occasional Operator"**—Total hysterectomy, as the operation of choice in the treatment of benign diseases of the uterus, has become increasingly popular during recent years. Hysterectomy with removal of the cervix is technically more difficult than without removal of the cervix, yet statistics from large gynecological clinics have shown the more radical operation to be little if any more dangerous. Gaston<sup>34</sup> raises the question as to whether the total operation should be advised for surgeons of limited experience. The recorded opinions of well-

trained pelvic surgeons are of but one conviction.

Gaston presents this paper in an effort to show that total hysterectomy may be safely utilized by the surgeon who does only an "occasional" hysterectomy if he be familiar with pelvic anatomy and with a satisfactory technic for removal of the cervix.

During a period of seven years, the author performed 110 abdominal hysterectomies, 71, or 64.5 per cent, of which were total. Six cases of total abdominal hysterectomy were performed for malignancy and were not included in this study. There were twenty-nine cases in the same period of supracervical hysterectomy. There was little morbidity difference in both groups. The most frequent postoperative complication encountered was cystitis occurring twice as frequently in the cases of supracervical than in the total hysterectomy group. During the past three years special post-operative attention has been given to the bladder with improved results. A constant urethral catheter drainage is maintained for a period of four to seven days after operation. The bladder is thoroughly irrigated three times daily with a *saturated aqueous* solution of *sulfanilamide* heated to body temperature. After removal of the drainage apparatus, the bladder is emptied with a catheter, introduced under rigid aseptic precautions, every six to eight hours, until the patient voids in amounts exceeding 6 ounces. Thereafter, catheterization of the bladder is done once daily until the residual urine is less than 1 ounce. *Sulfadiazine* in doses of 0.5 gm. are given by mouth four times daily, starting the day after operation and continuing until a day or two after catheterizations have been stopped.

Fifty-eight cases were followed for an average of 23.2 months. One case devel-

oped a postoperative ventral hernia. In a few cases, vaginal discharge persisted after operation. Removal of exuberant granulation tissue followed by cauterization with silver nitrate has in every case resulted in prompt and permanent healing. In four cases, evidence of slight shortening of the vaginal tube was present. There were no deaths following either total or supracervical hysterectomy done for benign disease. The technic used by Gaston in this series is that described by Meigs by which accurate hemostasis during removal of the cervix is easily obtained. This is the important single consideration in the entire operation. The importance of adequate vaginal preparation is emphasized. The uterus is routinely curetted prior to surgery, and if infection or malignant growth is present, the cervix is closed tightly with a suture. If a minor amount of perineal relaxation is present, this is repaired before laparotomy. If a large relaxation is present, it is deferred until after hysterectomy, the patient's condition permitting. Otherwise, the repair can be done at a later time. Total hysterectomy required 16.1 minutes longer of operative procedure than did the supracervical hysterectomy.

From a review of his cases, Gaston is of the opinion that the total operation can be safely utilized by the general surgeon of average experience.

**Preservation of Ovarian Tissue in the Treatment of Endometriosis**—Cashman<sup>18</sup> presents results in a series of 271 cases of endometriosis. Of these, 167, or 61.6 per cent, had hysterectomy performed with conservation of ovarian tissue. Since conservative operations in young women are disappointing in their results, frequently necessitating repeated operations; or when the generally accepted treatment by castration by radium is employed, with resultant pre-

mature and often severe menopausal manifestations, the author became interested in the conservation of ovarian tissue in the treatment of young women with endometriosis. The surgical procedure adopted is to remove the uterus and major lesions in the ovaries, if present, and disregard the implants and preserve all of the ovarian tissue possible. It is found that if the uterus is removed, no further trouble is experienced, and in none of the cases so treated has reoperation been necessary in the cases followed.

The rationale for this treatment was based upon the fact that when fibroids were accompanied by mild or moderate endometriosis and it was thought that the patient's symptoms were due chiefly to the fibroids, hysterectomy was done and one or both ovaries were left intact. The patient's symptoms disappeared and there was no evidence of extension of the endometriosis later. This happened so frequently that an explanation was sought. Failure of ovarian function does not seem to be the explanation for this, since there is adequate proof that ovarian function may continue years after hysterectomy. Cashman hopes to contribute the answer in the future.

Of 155 cases followed, in 11, or 71.6 per cent, ovarian tissue was conserved, whereas in 44, or 28.4 per cent, removal of all ovarian tissue or radium was used in the treatment of endometriosis. Although abdominal pain was the chief symptom in 65.3 per cent of the patients before operation, only 12 complained of abdominal pain and 4 of abdominal discomfort in the follow-up series. Seventy-nine and three-tenths per cent were well or had nonpelvic symptoms and only one patient stated she was unimproved after a conservative operation.

Hysterectomy with conservation of some ovarian tissue was done in eighty-

five cases, or 54.8 per cent, and in twenty-nine of them the uterus alone was removed. Hysterectomy relieved all of the menstrual symptoms and it was the experience of the author that abdominal pain and dyspareunia were also relieved clinically. The results have been as good as with the removal of all ovarian tissue and the menopause was not precipitated suddenly.

### Endometrium

**Adenocarcinoma—Results of Various Types of Treatment**—The results of treatment in the University of Minnesota Hospital of 225 patients with adenocarcinoma of the uterine corpus are reviewed by McLennan.<sup>35</sup> One hundred and eleven of these were seen more than five years ago. No patient had been lost in the follow-up program. Eighty of the 111 patients were treated primarily at the University Hospital, while 31 had some form of treatment elsewhere. Seventy-six of the 80 women not previously treated elsewhere were living and free from recurrence five years after treatment, giving a relative cure rate of 44.7 per cent. More than half of these (46) were treated by irradiation alone. Five others were treated initially with radium and x-ray, hysterectomy being done from one and one-half to six years later because of local recurrences. The reasons that irradiation alone was used in 46 cases were that 26 patients were considered inoperable on the basis of actual or possible extension of carcinoma beyond the uterine corpus; 7 patients were over seventy years of age; 5 had diabetes mellitus; 2 had pelvic inflammation following radium; in 2 cases, corpus tumor was mistaken for primary cervical tumor; 2 patients had heart disease; 1 had a carbuncle of the abdominal wall, and 1 patient weighed 330 pounds and had a hypertension.

From 1939 to 1943 inclusive, 114 new patients with carcinoma of the uterine body were observed, 21 of whom had been subjected to therapy elsewhere. From the beginning of 1939 until July 1, 1941, routine therapy for carcinoma of the corpus consisted of deep x-ray, intrauterine radium, and total hysterectomy in that order. The dosage of **x-ray** amounted to 250 to 300 per cent skin erythema dose delivered to the site of the tumor in twenty five to thirty daily treatments over approximately four weeks. **Radium** then was applied from five intrauterine portals, and a dose of 5000 mg. hours was given over a period of 100 hours. Four to six weeks later total hysterectomy and bilateral salpingo-oophorectomy were carried out by the abdominal route. Only 53 per cent of the patients received "routine" treatment, it being necessary to interrupt this planned sequence of treatment for various reasons. Only one patient, receiving "routine" treatment thus far has died from recurrent carcinoma. Only one fourth of the patients receiving incomplete therapy have survived from 0 to 4 years, so that the ultimate survival group may be expected to be exceedingly low.

The absolute five year cure rate has been 45 per cent, including certain patients previously treated elsewhere. The exclusion of these latter patients did not improve the results. Poor results are shown to follow routine use of radium and x-ray alone. McLennan is of the opinion that certain patients so treated may be salvaged even many years later by hysterectomy for recurrent or perhaps persistent carcinoma. Good results have followed the use of total hysterectomy, with or without preoperative or postoperative irradiation. The operative mortality for the entire series was 5.8 per cent uncorrected or 3 per cent cor-

rected. McLennan concludes with opinion "the final results in the treatment of carcinoma of the uterine corpus are predetermined to a considerable extent by the nature of the material presented for therapy, in terms of metastases, medical and surgical complications, age, weight, and nutritional status."

## URINARY SYSTEM

### Gynecologic Disorders

#### Influence on the Urinary System—

One of the most important factors in the production of urinary tract changes is pressure exerted by pathologic processes arising in the female pelvis. Hundley and Diehl<sup>36</sup> review briefly the physiologic and pathologic changes in the urinary tract during pregnancy and emphasize the effects of estrogen and progestogens on ureteral activity. Quite similar dilatation changes in the urinary tract occur in the presence of large pelvic tumors; however, the hormonal manifestations present in pregnancy are not observed.

The pathology of the urinary tract as a result of parturition following relaxations of the pelvic floor with special reference to cystocele and the frequent associated cystitis is discussed. Uterine prolapse may be an etiologic factor in the production of dilatation of the ureter. The authors present a technic for the closure of large vesicovaginal fistulae, in which the surrounding vaginal mucosa is used to cover the defect.

Stress incontinence is of frequent occurrence in the postmenopausal woman with regressive changes occurring in the bladder and trigone due to absence of estrogenic stimulation. Trigonitis is frequently associated with these regressive changes and is usually alleviated by the topical application of *silver nitrate*

solution, 2 or 3 per cent, through the Kelly cystoscope. Stress incontinence is also seen as a result of obstetric trauma when there is an associated relaxation and stretching of the fascial supports. The operation devised by Kelly is of distinct value, and its success is dependent on the proper buttressing of the vesical neck.

There is no doubt that chronic disease of the adnexa, with or without masses, causes pressure on the ureter and by inflammatory invasion produces strictures of the ureter. The work of Schreiber on ureteral stricture showed that adnexal disease was one of the most frequent etiologic factors in its production. In an attempt to determine the rôle of cervical infections in the production of bladder disease, Hundley and Diehl cystoscoped fifty women with varying degrees of endocervicitis. From these studies, the authors are of the opinion that endocervicitis plays a very unimportant rôle in the production of bladder infections. Cystoscopy of 413 patients with carcinoma of the cervix disclosed bladder involvement in only 54, or an incidence of 13.1 per cent.

Endometriosis involving the bladder is of common occurrence, and when hematuria occurs at the time of menstruation, a diagnosis can be readily made. The development and maintenance of this ectopic endometrium is dependent on ovarian activity. When there is widespread involvement of the intestine, rectovaginal septum, or bladder, oophorectomy may be the procedure of choice, thus avoiding a difficult and often hazardous operation.

**Female Urethra—*The Connecting Link Between the Urologist and the Gynecologist***—Folsom and O'Brien,<sup>37</sup> together with other workers, have proved that there exists a definite group of glands surrounding the posterior part

of the female urethra, that this group of glands is identical in morphology, distribution, secretory activity, and location with the male prostate and that, in fact, this group of glands should and will ultimately be spoken of as the female prostate. These glands do become infected in very early infancy and may remain infected for many years or even throughout life, producing a varied and, at times, a bizarre papillary posterior urethritis. This process may be acute, subacute, or chronic. In many cases the urethral lumen may be strictured. The severe papillary or granular posterior urethritis and the stricture go hand in hand to produce a clinical entity which can and does cause many women untold suffering.

There are two groups of clinical symptoms that are produced by this inflammatory posterior urethritis, bladder irritation and pain, and these two cannot be overemphasized; for so many women suffer from frequency, burning, and some type of pain around the pelvis that it becomes of real importance in treating women. Ninety per cent of all women with urologic complaints have this bladder irritation as one of the presenting complaints.

Among women with the complaint of bladder irritation, many errors in diagnosis and treatment have been made. Some have been accused of being neurotic, others have had uterine suspension operations, and cystocele repairs with a persistence of symptoms until the posterior urethritis has been cured.

The second symptom produced by this condition is referred pain. The most frequent sites are either in the right or left iliac region; low down, the lumbosacral region of the back; either loin, where if the pain is severe it may be, and has frequently been, mistaken for renal or

ureteral disorder; and the inner side of the thigh.

The foundation work of the treatment of this troublesome pathologic condition is *urethral dilatation*. This should be done twice a week regularly, beginning with the size sound that will stretch but not tear the urethral mucosa. Then the size of the sound should be gradually increased until a 30 or 32 F. will go easily. After each dilatation, 10 to 15 cc. of 0.25 per cent solution of strong *protein silver* is instilled into the urethra. When the urethra has been dilated for about six weeks, the pathologic tissue in the posterior urethra is fulgurated, after which the patient is permitted to rest for two weeks. Then the dilatations are resumed for a period of six to eight weeks, when another fulguration is done. This routine is followed until the patient is relieved and there is no further evidence of pathologic change present in the posterior urethra.

In some cases that are refractory to treatment, one should never lose sight of the fact that there is a very intimate lymphatic connection between the cervix uteri and the posterior urethra and trigone. Hence these patients may be and often are helped by clearing up an old endocervicitis, which may have been playing a part in the perpetuation of the urethral infection.

**Stress Incontinence** *Use of Transplanted Abdominal Fascia in the Relief of*—In the majority of cases, stress incontinence is so slight that it constitutes only a minor annoyance. It sometimes develops to such a degree that the patient, on the slightest muscular effort, discharges large quantities of urine. Such individuals are only continent when lying down or sitting quietly and, even under these circumstances, as can be readily demonstrated on the examining table.

there is lack of urinary control if the intra-abdominal pressure is raised. It is with this extreme degree of stress incontinence, particularly if previous surgical efforts at relief have failed, that this report is chiefly concerned.

The etiological factors in the background of this condition are well known, consisting most commonly of the injuries which occur to the supporting structures of the pelvic organs during parturition. If such injury is concentrated on the supporting tissues of the bladder neck and upper urethra, stress incontinence will appear almost immediately. On the other hand, if the injury is mostly to the supporting structures of the posterior part of the bladder trigone, the symptom may not appear until many years later, usually at about the time of the menopause. This is the most common sequence of events. The etiological factors in summary may be traumatic, involutional or hormonal, congenital, or a combination of two or more of these factors.

The physical characteristics of women suffering from severe stress incontinence are surprisingly similar. In order to prevent urinary leakage, they avoid physical activity as much as possible, and, therefore, tend to become adipose and flabby. This tendency does not improve their risks as surgical patients. Only by relieving the patient of her disability can she be made more active, thereby improving her general condition.

Studdiford<sup>28</sup> reviews in detail the supporting mechanism of the female urethra and bladder. It seems evident that the lesion permitting the development of urethrocele must consist in the sudden tearing or gradual attenuation of the most anterior part of the pubocervical fascia, together with its descending investment on the urethra, thus allowing the bladder neck and urethra to herniate downward and backward through the

defect. Cystoscopic observation suggests that the posterior segment of these structures is mainly involved.

With the development of a urethrocele consequent on injury to or inadequacy of the supporting structure, the normal sphincter mechanism becomes subject to additional forces. Even the slightest increase of intra-abdominal pressure must cause some movement downward and backward of the anterior trigone. This constant tug on the circular muscle of the internal sphincter results in its loss of tone. When sharp increase in intra-abdominal pressure takes place, the anterior trigone herniates through the defect, pulling open the posterior segment of the internal orifice by overcoming the internal sphincter. The resultant incontinence of the internal sphincter accounts for the sudden escape of urine under propulsion of the increased intra-abdominal pressure and the normal tone of the detrusor muscle. When intra-abdominal pressure falls, the trigone rises, releasing the internal sphincter which once more becomes competent.

The author is of the opinion that the success of the Kelly operation is due to the unconscious inclusion of the supporting structures about the upper urethra and bladder in his repair. There are three possible explanations for the causes of operative failure in stress incontinence: First, that the operative procedure has been inadequate; second, that the healing process has been imperfect due to infection or faulty blood supply, and, third, that the supporting tissues utilized in the repair are so attenuated that they once more give way under the continual assault of intra-abdominal pressure. Since the last explanation is the most plausible, the possibility of transplanting tissue from another source should be considered.

Experience gained in the use of transplanted abdominal fascia in combination with vaginal plastic operations upon the upper urethra and bladder neck is the basis for this procedure.

The author presents two technical procedures utilized in patients with previous operative failures. Briefly, the technic of procedure one includes the following steps:

A long incision is made in the abdominal wall with its center about 2 to 3 cm. above the upper border of the symphysis and curving upward on each side of the midline to a point slightly above the anterior superior iliac spines. It extends down to the aponeurosis of both the external oblique and the external rectus sheath. The aponeurosis of both the external oblique and internal oblique is incised longitudinally for a distance of 1.5 to 2 cm. at the lateral extremity of the skin incision. The inner surface of the internal oblique aponeurosis medial to this incision is freed from the underlying muscle. Beginning at each angle of the incision, a strip of the combined aponeurosis is mobilized by means of two parallel incisions extending downward and medially to a point about 1.5 to 2 cm. of the midline. A similar strip is then obtained from the opposite side. The defect in the aponeurosis is closed up to the border of the rectus muscle with a running No. 1 chromic catgut suture, care being taken to include both the internal and external layers. Traction sutures are then passed through the tips of the aponeurotic strips and held by small clamps.

The patient is then put in the lithotomy position. The anterior vaginal wall is seized with two low Alis clamps, placed as far laterally to the midline as possible and at as high a level as can be obtained, and a transverse incision is made through the depth of the vaginal wall. Scissor dissection defines the plane between the bladder and vaginal wall. The vaginal wall is then divided in the midline at right angles to the incision to a point about 1 cm. from the urethra. The plane of the supporting fascia of the bladder neck and upper urethra is then identified and with blunt dissection, the finger is inserted into the space of Retzius. The supporting fascia of the upper urethra and bladder neck is then plicated by means of interrupted mattress sutures. If marked relaxation is present, a second layer of such sutures can be added. The operator then passes a uterine forceps lat-

eral to the bladder neck into the space of Retzius grasping the traction suture placed at the tip of the aponeurotic strip and pulled through. This is repeated on the other side and both strips tied together by tying the traction suture, thus forming a sling about the bladder neck. The vaginal mucosa is then closed with interrupted sutures and the abdominal incision is closed.

This procedure has been used on ten patients with gratifying results.

The second operative procedure was used for patients who required both abdominal and plastic surgery and involves total abdominal hysterectomy combined with transplantation of fascial strips in principle as outlined in the previous technic. This procedure was performed on three patients with satisfactory results.

Only eighteen months have lapsed since the first operation was performed upon these thirteen patients. Studdiford feels that at least five years with freedom of stress incontinence must elapse before a permanent cure can be assumed.

**Prolapse of the Urethra** *The Hepburn Operation* The objective of the author<sup>30</sup> is to bring to the attention of the gynecologists a simple and useful procedure for the cure of prolapse of the urethra. The original technic is presented:

"Fill the bladder. Make a suprapubic incision. Put a suture in the bladder so it can be used as a retractor. Work the finger down in the prevesical space under the arch of the pubis. When the neck of the bladder and urethra are freed up enough, draw on the bladder traction suture. The prolapse will be seen to disappear as soon as this traction is made. Then, with a curved needle and No. 2 chromic catgut, anchor the neck of the bladder to the periosteum of the pubic arch. Be sure that retraction and anchoring are sufficient so that downward pressure with the hand on the full bladder does not produce any sign of prolapse. Drain prevesical space, if deemed necessary, for twenty four hours."

The author presents three case reports treated successfully by this operation.



**Vesicovaginal Fistula — A Series of Forty Cases.**—Vesicovaginal fistulas are classified by the author,<sup>40</sup> dependent upon their location under three heads. A fistula may lie in the vagina at an appreciable distance from the cervix and from the internal urinary meatus; a midvaginal fistula. It may be adjacent to the cervix, when scar tissue fixes it to that structure; a juxtacervical fistula. It may be near to, or actually involve, the internal urinary meatus or even the urethra, a part or whole of which may have sloughed away; this it is convenient to call a juxtaurethra fistula. In this series of forty cases observed during the past six years, eighteen were juxtacervical, five midvaginal, and seventeen juxtaurethral fistulas. All the juxtacervical and midvaginal fistulas were operable, but two of the juxtacervical cases were unfit for surgery because of their poor general condition.

Of the seventeen cases of juxtaurethral fistulas, three were unfit for operation because of their poor local and general condition. Of the remaining fourteen cases, two were regarded as inoperable because in each case a large part of the inferior border of the fistula was bone, the os pubis, and it seemed impossible to mobilize the bladder. Of the total of forty cases, thirty-five submitted to treatment and twenty-eight were cured, twenty-five by the flap method, and three by other means.

The author prefers a period of at least three months to elapse from the last labor or previous operation before a repair is attempted. An intraspinal anesthesia of light procaine is ideal and lasts long enough, a point of importance as a difficult case may take two or three hours to complete. An incision is made from below upwards to the fistula through the vaginal skin, and then from the fistula upwards to the cervix, except in

juxtacervical fistulas. Then by inserting a curved Mayo's scissors into the fascial space between the vagina and bladder and opening the blades, the separation between bladder and vagina is easily obtained. This is done through both incisions until the vagina and bladder are held together only by the adherent margins of the fistula. In juxtacervical fistulas, the incision above the fistula is made transversely; and procedure can be simplified by carrying the paravaginal incision right up to the fistula itself. The fistula is then freed by cutting over a probe against the scar tissue which still binds the bladder and vagina together at its margin. In the juxtacervical fistulas and in the larger midvaginal ones, and even in some of the juxtaurethral fistulas, it is necessary to mobilize the bladder so that the fistula may be closed without any tension. The bladder opening is then sutured very meticulously avoiding the mucosa. This suture line is then tested for leakage by inflating the bladder with methylene blue solution. The vaginal mucosa is then carefully sutured, and a catheter placed in the bladder is sutured to the labia minora. Postoperatively, the catheter is left in for twelve days, extreme caution being observed that no stoppages occur in the catheter, which is cleared by injecting 5 to 10 cc. of sterile water. Should the patient become pregnant, cesarean section is recommended in patients who have had successful repairs of previous vesicovaginal fistulas.

**Ureterosigmoidostomy, or Plastic Repair**—Thompson<sup>41</sup> is of the opinion that the actual cause of vesicovaginal fistula is prolonged pressure of the fetal head on the soft parts with cutting off of the blood supply and subsequent necrosis, especially if the bladder is distended. All forty-two cases in this series occurred after labor.

The size of the fistula was pinpoint in two cases; small (not more than one-half inch in diameter) in eight cases; medium size (one-half inch plus) in eight cases; medium size and at the neck of the bladder in seven cases; large or very large in fifteen cases, and slitlike and situated high up behind the symphysis in two cases. In these last two cases, and in seven of those classed as large, the urethra was partially or completely destroyed.

The important points in performing a vaginal plastic repair operation are (1) preliminary clearing up of infection; (2) excision of scar tissue; (3) mobilization of the bladder wall; (4) closure of the fistula without tension; (5) hemostasis; (6) drainage of the bladder to prevent overdilatation and strain on the repair site.

In all, twenty-seven cases were treated by attempts at plastic repair, being considered operable. Seventeen, or 63 per cent, were cured; three, or 11 per cent, were improved; in six, or 22 per cent, the operation failed, and one, or 4 per cent, died following the operation. The causes of inoperability or failure are large size, difficulty of approach, destruction of the urethra, gross destruction of tissue, especially of the bladder wall and fistulas at the neck of the bladder with the urethra torn away. Much scar tissue in the wall of the bladder makes healing difficult and infection hinders successful cure. Postoperative hemorrhage usually spells failure of the operation.

The most effective method of treating inoperable cases is by transplanting the ureters into the large bowel, usually the sigmoid colon. In this series, thirteen cases were treated by ureterosigmoidostomy, nine in two stages, and four at a single operation. Five of the thirteen patients died, a mortality of 38.5 per cent. The author is of the opinion that

improvements in technic should be sought by a review of fatalities to reduce this very huge mortality rate in ureterosigmoidostomy.

**Vesicovaginal and Urethrovesicovaginal Fistulas—Operative Technic**—This article is based upon sixteen years' experience in the treatment of vesicovaginal and urethrovaginal fistula and is presented with the objective of assisting the "intermittent" operator to obtain good results in the treatment of these conditions. A careful preliminary study of the fistula is essential.

Simple fistulas involving the bladder and free from, or with slight, fibrosis, are easily cured by adopting the principles to be presented. Complicated fistulas present greater difficulties owing to their varied nature as a result of destruction of tissue and resulting fibrosis. Any or all of the following complications may be present: Stenosis of the vagina in all degrees, the most severe being when the normal vaginal walls are replaced by rigid fibrous tissue and the orifice admits one finger; or partial stenosis, the result of patchy fibrosis; fibrous bands, the commonest being a transverse band at the junction of the upper and middle thirds of the vagina, causing an hour-glass contraction, in the upper portion of which is the cervix and often the obscured fistula. The size of the fistula varies from pinpoint to the whole vault of the vagina, in which case the bladder is prolapsed. The shape varies considerably and is governed by the site and amount of fibrous tissue. The position of a fistula is not constant. It may be central and easily accessible, or high up behind the symphysis. Mobility of the cervix is often impaired and, in some cases, the cervix is completely immobilized by a solid mass of fibrous tissue, thus considerably increasing the difficulties of obtaining a good exposure. Finally,

the urethra may have been destroyed in part or, rarer, in its entirety.

The large majority of fistulas can be cured by one operation (of eighty-five operations, seventy-eight were one-stage). With large fistulas, a two-stage operation, based on reducing the size of fistula, is worth considering. The position of the patient at operation should be in 15 degrees lithotomy with the vulva at about eye level. In the complicated cases, a Schuchardt's incision will often be necessary to provide exposure. Hemorrhage during operation is usually considerable. Infiltration of the operation area with adrenalin reduces the amount of bleeding. Any visible bleeding point is controlled by underpinning with needle and catgut.

The principles and steps of operation are the following:

Incision of vaginal mucous membrane and exposure of the fistula or urethra or both. The first cut around the fistula is made about  $\frac{1}{10}$  inch from the edge with the object of marking out the incision. Joining this an incision over the urethra and one toward the cervix are then made. This incision is deepened, and the vaginal mucosa on both sides is separated up to the incision over the urethra. The vaginal mucosa is next separated from the urethra and the flaps enlarged and sutured to the labia minora. The fistula is then completely mobilized. When the urethra is destroyed, special care is required for restoration. If one-third inch of urethra is available, it can be elongated after mobilization and attached to the bladder with perfect functional results. A successful result will depend upon careful planning of the incision, special mobilization and suturing. The edges of the fistula must always be inverted before suturing. The standard suture is placed vertically as by this means it is easier to reduce the lumen of a dilated urethra and to plicate the bladder in the region of the new internal sphincter. Every effort should be made to insert a second Lembert suture or to cover and reinforce the first suture line with borrowed tissue. Hayes<sup>42</sup> inserts a No. 8 rubber urethral catheter before or after closure of the fistula. Plication sutures in the region of the bladder-urethra area are then

inserted until a fairly tight fit is obtained. If it is deemed necessary, the urethra is then plicated. Interrupted sutures are inserted in the vaginal mucosa and the vagina is tightly packed with gauze, which is removed after eight hours. Two principles of postoperative treatment rigidly enforced are keeping the bladder empty and the sutures clean.

If second operations are required after a failure, Hayes prefers to wait six months, because fistulas resulting from an attempt at repair contract to a remarkable degree. Of a total of eighty-five cases of complicated vesicovaginal and urethrovesicovaginal fistulas operated upon, seventy-three were cured, three partially cured, seven were considered failures, and two patients died, a mortality of 2.35 per cent. Eight patients required a second operation. The percentage cure rate was 89.85 per cent, which, considering the variety and complications encountered, is adequate proof that the flap-splitting operation is a satisfactory operative method.

**Urethral Caruncles—Rate of Recurrence**—A series of eighty-five cases<sup>43</sup> of urethral caruncle, treated over a period of fifteen years ending two years ago, is reviewed to determine the likelihood of recurrence developing after treatment and the period of time during which a recurrence remains a possibility. Sixty-eight cases were treated by excision of the caruncle and the caruncle-bearing area of the posterior lip of the urinary meatus. The caruncle returned in twenty-seven of these patients within a period of one to fifteen years. Fifteen patients were treated by coagulation diathermy. To the present time there have been no recurrences. This is probably due to the fact that the fibrosis following the coagulation inactivates the caruncle-bearing area of the posterior meatal lip. An electrocautery was used to burn off the caruncle base after excision in six cases, but recurrence occurred in

three of these. Radium was used in three cases but with questionable effect and was abandoned. It would seem that the radiosensitivity of a caruncle is no greater than that of the urethral mucosa from which it springs, and to gain a successful result with radium means pushing the dose to the limits of the tolerance of the urethral mucosa and incurring the risks of a persistent burn.

Thus far, the best results in the treatment of urethral caruncle is by coagulation diathermy.

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## OBSTETRICS

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### ABORTION

#### Postabortal Peritonitis (Pathogenesis)

During the past fifteen years, study of the clinical and pathologic aspects of incomplete abortion has been conducted by Falk<sup>1</sup> and his associates at the Harlem Hospital in New York. From this

study, two conclusions were reached. First, the uterine cavity is usually infected in incomplete abortions, whether spontaneous or induced, with or without fever. Second, all infected abortions may be divided into six groups, depending on the pathology found and their clinical course.

These six groups are:

1. Abortion in which the infection is limited to the cavity of the uterus, which comprises 83 per cent of all abortions seen.

2. Abortion in which the infection spreads from the uterus but is still limited to the extraperitoneal structures. About 9 per cent of all abortions are of this group, which includes parametritis, pelvic cellulitis, extraperitoneal pelvic abscess, perivesical and perirectal exudates, etc.

3. Abortion in which the infection spreads from the uterus to the veins and where the predominant symptoms are the result of thrombophlebitis, with or without embolization. Parametritis is frequently an associated or causative lesion.

4. Abortion in which pathogenic bacteria have left the uterus and become secondarily implanted on the mural endocardium, heart valves, or pulmonary artery, and the infection is disseminated from this location. Visible evidence of either a preexisting pregnancy or of infection in the uterus is often absent at autopsy.

5. Abortion in which the infection spreads from the uterus to the peritoneum, producing a general peritonitis.

6. Those cases in which the uterus has been perforated by an instrument. The pathologic findings depend upon the degree of infection, asepsis, trauma to adjacent organs, etc.

This present study is devoted to an analysis of the pathogenesis and the associated pathologic findings in the fifth group, *i. e.*, general peritonitis.

In postabortal disease, the infectious process begins almost exclusively at the placental site and in the adjacent endometrium. This area is the seat of a suppurative process and may be converted in whole or in part into a shaggy, in-

flamed, or necrotic membrane to which portions of placenta, decidua, and blood are adherent.

How does the infection extend from the uterus to the peritoneum? In this series of sixty-one cases of postabortal peritonitis, all cases presented an endometritis of varying severity. The infection spread from the endometrium to the peritoneum as a result of:

1. Direct extension through the tubes seemed to be the pathway of infection in forty, or 66 per cent.

2. Extension of the infection from a parametritis to the peritoneum occurred in six cases, or 10 per cent. In one case, the peritonitis was caused by a rupture of a broad ligament abscess into the peritoneal cavity.

3. The infection extended through the myometrium in four, or 7 per cent, of the cases.

Other combinations occurred in ten patients as follows: In six patients, endometritis, salpingitis, parametritis, and peritonitis were present. The pathway of infection was not clear. In four patients, endometritis, abscess of the myometrium, salpingitis, and peritonitis occurred. It is probable that in this group the tubes were the chief pathways of extension as the myometrium contained discrete abscesses with no contiguous inflammation of the enveloping peritoneum. These cases are not included in the first group because of the questionable etiology of the peritonitis.

Ovarian abscess was found seventeen times, an incidence of 28 per cent. Thrombophlebitis of the uterine or ovarian veins, or of both, occurred in twenty, or 33 per cent of all the patients observed.

### Habitual Abortion—Therapy

Vaux and Rakoff<sup>2</sup> review the causes of habitual abortion. Among these are:

1. Abnormalities of the ovum resulting from defects inherent in the germ plasm.

2. Maternal factors which influence pregnancy, such as inflammatory disease or tumors of the pelvic organs, febrile diseases, maternal syphilis, malnutrition, avitaminoses, incompatibility of blood types (particularly of the Rh factor), thyroid dysfunction, and deficiencies of the hormones produced by the corpus luteum and the placenta during pregnancy.

3. External factors, as chemical poisoning, x-rays and radium, and trauma.

4. Abnormalities of the male germ plasm and constitutional diseases of the male.

Many of these pregnancies can be saved and carried to term with the birth of normal babies, confirming the viewpoint that these malformations may often result from external factors which have interfered with the growth, development, or nutrition of the embryo.

The authors have been impressed not only by the high percentage of habitual aborters who exhibit low pregnandiol titers but even more by the frequency with which these are associated with diminished blood and urine estrogen levels. These findings have encouraged the authors during the past three years to treat habitual aborters with combined *estrogen-progesterone therapy*.

A study was made of a group of twenty-four patients with habitual abortion who were treated with estrogen and progesterone. These patients had gone through a total of eighty previous pregnancies from which there had resulted only seven living babies (8 per cent). There had been fifty-two abortions, eighteen miscarriages, two stillbirths, and one premature live birth in which the infant did not survive.

Fifty-four per cent of this group had no difficulty in becoming pregnant, 8 per cent were of diminished fertility, and thirty-eight per cent were of poor fertility. In none of these patients were there any pelvic abnormalities or systemic diseases which would influence abortion. In only one patient was the basal metabolic rate diminished.

Two patients had Rh incompatibilities (Rh-negative wife and Rh-positive husband). One of these delivered a normal living baby and the other aborted; in neither case did Rh antibodies develop.

Examination of the endometrium obtained by biopsy or curettage was available in eleven cases before the present pregnancy. Good secretory function was noted in seven cases, impaired secretory function in two, and an interval endometrium in two.

Urine hormone assays were made in fifteen cases prior to the onset of pregnancy. Urine gonadotropin assays made at the midcycle were normal in 87 per cent. Urine estrogens made at the midcycle and during the third week of the cycle were diminished in 67 per cent, while low or absent pregnandiol values were obtained in 53 per cent. Since these studies were made in only one cycle, the authors indicate that their significance is limited.

Hormone assays consisting of urine pregnandiol determinations, serum estrogens, and serum gonadotropins were made early in pregnancy in nineteen cases. In almost all of the cases, one or more additional assays were made and in three cases monthly assays were done.

On the initial assay, 95 per cent of the cases showed normal serum gonadotropins. Seventy-nine per cent had diminished serum estrogens and 83 per cent had diminished pregnandiol titers. In thirteen of the nineteen cases studied, both

estrogen and pregnandiol were diminished. These findings indicate a deficiency of the corpus luteum during the early weeks of gestation and an inadequacy of the placenta to take over its functions.

**Method**—During the pregnancy all patients were treated by the injection of *progesterone*, 10 mg., and *alpha-estradiol benzoate*, 10,000 rat units, given together two or three times weekly. This treatment was generally continued to the period of viability or later.

There was fetal salvage of sixteen babies, or 67 per cent. There were fifteen full-term live births (with one neonatal death due to congenital abnormalities), three premature live births, of which two survived, two miscarriages, and four abortions.

In our opinion, the authors have achieved an unusually high salvage. Their results represent the best thus far in the treatment of habitual abortion. By this method the editor recently succeeded in delivering at full term for the first time a patient who had had nineteen previous miscarriages.

Ingram<sup>3</sup> reports six cases of habitual abortion in which a combination of mixed tocopherols (tocopherex) and oral pregnenolone (pranone) proved successful. The author advises that treatment must be begun before the onset of any signs of threatened abortion, preferably as soon as the first period is missed or, better yet, as soon as pregnancy is attempted.

This treatment is to be used in conjunction with, but not to replace, other indicated corrective measures. It is interesting to note, however, that no sedatives nor narcotics were found necessary. No ill effects were observed, and all babies were normal. This treatment is for the particular pregnancy, and probably will have no beneficial effects upon any future pregnancy. It seems to be worth trying for the patient who cannot obtain the hormones by injection.

### Spontaneous Abortion

Spontaneous abortion is said to occur in the ratio of one to every six confinements. Hudson and Rucker<sup>4</sup> in 1000 consecutive pregnancies found 94 spontaneous and 68 threatened abortions. Treatment with *bed rest* and *progesterone* was followed by recovery in 43 per cent. However, 3 patients who were treated successfully had deformed babies (1 microcephalus and 2 spina bifidas). Falls and intercurrent infections were of no etiologic consequence in this series. Pelvic inflammatory disease was encountered only three times, but 2 of these patients aborted. One of the 4 patients with uterine fibroids aborted. Two of 8 diabetic patients aborted spontaneously. Overweight patients and those with low basal metabolic rates seem to be rather prone to abort. The same is true of patients who give the history of sterility.

Forty-four and one-tenth per cent of the patients who aborted had retrodisplacement of the uterus on postpartum examination as compared with 26.9 per cent of those who had term deliveries.

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## PREGNANCY

### Hyperemia

A rapid pregnancy test which he terms the hyperemia test is described by Zondek<sup>5</sup> and his co-workers. The authors call attention to the fact that chorionic gonadotropin brings on, in the ovary of rodents, the well-known anterior pituitary reactions (I to III). The earliest of these reactions is hyperemia of the ovary of the infantile rat. Hyperemia occurs as early as two to six hours after injection, reaches its peak after twenty-four hours, and disappears in forty-eight hours. Hyperemia is the first stage of anterior pituitary reaction II, its second

stage being the follicle hemorrhage (blood dot).

As regards the hyperemia effect (anterior pituitary reaction II) in the rat, the gonadotropic hormone from the anterior pituitary lobe is the most active, pregnant mare blood gonadotropin is the least active, and the activity of chorionic gonadotropin from pregnancy urine lies in between. With chorionic gonadotropin, hyperemia may be produced with the same amount of hormone which evokes vaginal estrus; the amount used for luteinization is about three times as great.

Hyperemia is apparently evoked by the luteinizing hormone, while the follicle-stimulating hormone seems to play a rôle as an augmenting factor.

The hyperemia hormone pregnancy test in the infantile rat may be used for the early determination of pregnancy. The time factor plays a decisive part. In the two-hour test, the reaction is extremely unreliable, so that pregnancy can be diagnosed in only 69 per cent of the cases and with the six-hour test in 92.2 per cent, whereas the twenty-four-hour test is reliable in 100 per cent of the positive cases. There may be, however, occasional positive results with the twenty-four-hour test with nonpregnant patients (tumors). They bring the error in the twenty-four-hour test to 1 per cent (tested in 300 cases). The two- and six-hour tests can be relied on if the result is positive. When it is negative, the result of the twenty-four-hour test must be awaited.

The hyperemia test in the infantile rat is suitable in undisturbed pregnancies. In cases of disturbed pregnancy (ruptured extrauterine pregnancy, threatened, incomplete or missed abortion, hydatidiform mole, and chorionepithelioma), the ordinary hormone pregnancy test cannot be dispensed with for the time being.

**Technic**—The routine technic is as follows: Three infantile female rats, three to five weeks old, weighing 20 to 25 gm., are used for every examination. They receive 4 cc. of urine each in two injections of 2 cc. at an interval of one hour. Injections are given subcutaneously into the neck. One rat is killed after six hours and the other two are killed in twenty four hours. The reaction is positive if hyperemia appears in at least one ovary of two different rats. As a rule all ovaries react similarly. The rats are killed and the uterine cornua lifted with a forceps. The ovaries are often covered with fat. In this case they should be turned and the fat is carefully teased away, any lesion being avoided which may cause hemorrhage. Comparison should be made with the color of the spleen or kidney. If the reaction is positive, the ovaries are slightly brighter than these organs, nearly strawberry red. The hyperemia should extend to the whole ovary and not only to single follicles. The operator should be able to distinguish red clearly.

### Weight Gain

The relationship of maternal weight gain and weight of newborn infants was studied by Beilly and Kurland.<sup>6</sup>

The relationship between mother's weight gain and the weight of the baby at birth has been examined from the data of 979 parturient cases. The average mother's gain was 22.28 pounds; the average weight of the baby was 7 pounds, 3 ounces.

There is correlation between the weight gain of the mother and the weight of the baby at birth. Although the degree of correlation is low, it is nevertheless significant. There is a 68 per cent probability that the baby's birth weight can be predicted on the basis of the mother's gain, within a range of plus or minus 0.9 pound of the estimated figure.

The size of the mother influences the weight gain during pregnancy. The light women show a larger gain. The heavier women show a smaller gain than the light. Heavier women tend to bear heavier offspring.



### Nutrition

The nutrition requirements in pregnancy are discussed by Lund.<sup>7</sup>

Studies attempting to determine the dietary requirements during pregnancy fail to take into account the problem of storage. It is clear that the pregnant woman stores many substances to a degree beyond the requirements of herself and her fetus as a reserve for emergencies. If these emergencies fail to develop, the excess is excreted during the puerperium. Water is an excellent example, as is nitrogen and probably iron, calcium, vitamin A, and others. For this and other reasons we must be very cautious in classifying the diet of any pregnant woman within narrow limits and hesitant to make dogmatic statements concerning minor deviations.

**Calories** — The average pregnant woman requires about 2500 calories per day during pregnancy. If for purposes of weight reduction the calories are limited to less than 2000, dietary supplements of minerals and vitamins may become necessary, depending on the foods deleted.

**Protein** — At least one moderately large serving of meat daily and liver once each week is important. The type of protein must also be considered and half or more should be grade A, which is that of animal origin, such as meat, milk, and eggs. There is no place for restriction of proteins in pregnancy, whether normal or complicated.

**Calcium and Phosphorus** — A negative calcium balance does not ordinarily occur if 1.5 gm. of native calcium is ingested each day. This amount of calcium not only supplies fetal needs but also permits the mother to gain calcium during the entire gestation. One quart of milk daily supplies 1.2 gm., nearly the normal requirement; the slight remainder is readily available in other

foods. There is no need for supplements of calcium. Calcium salts differ in the amount of calcium yielded. To equal the calcium obtained from a quart of milk, it would be necessary to take 8 gm. of dicalcium phosphate or calcium lactate or about 12 gm. of the gluconate salt. The amount of vitamin D necessary for adult mineral metabolism is not known. The Nutrition Council has empirically advised 500 to 800 units daily for pregnancy.

**Iron** — A daily intake of 15 mg. of iron will produce a positive balance in most women. Again it is possible to supply these needs by diet alone if the woman does not enter pregnancy with a deficiency. This is of considerable importance for not a few women begin with an iron deficiency due to chronic blood loss in the presence of a low intake. Determination of hemoglobin level during early pregnancy is essential and gives a very rough estimate of the dietary state as concerns this element.

**Vitamin A** — The authors' studies suggest that diet alone may not be sufficient during the last half of pregnancy; at least diet alone did not always maintain optimal plasma values. The addition of 5000 international units of vitamin A during the second trimester and 10,000 international units during the third trimester provided ample amounts for the maintenance of best possible plasma levels.

**Vitamin B Complex** — The importance of this group of water soluble substances cannot be denied. They are poorly stored, usually rapidly excreted and consequently must be continually replaced. At least a dozen separate factors of the B complex have been described. Adequate amounts of all can be supplied by diet alone and should be supplied in that manner if possible.

It is common practice to administer 1 to 2 mg. of vitamin K during labor,

not for maternal needs, but to build up fetal values for the critical early neonatal period. This is probably a justifiable practice.

Too little attention has been given the nutritional deficiencies produced by the complications of pregnancy. Regardless of cause, prolonged and severe vomiting of pregnancy produces starvation. Aside from fluids and electrolytes, one of the earliest deficiencies is in vitamins B and C. A vicious cycle may be set up by the administration of glucose parenterally, for the metabolism of glucose requires thiamine hydrochloride. The sudden exhibition of ample amounts of glucose quickly uses any remaining thiamine, thus precipitating an even greater deficiency. The grade of the deficiency depends on the duration and severity of the emesis. All grades occur. Occasionally, the author has seen such severe manifestations as polyneuritis, Korsakoff's psychosis, beriberi, severe glossitis, and even pharyngitis. He has also observed plasma vitamin C depleted to zero with clinical manifestations of scurvy.

In three cases of severe hyperemesis gravidarum, retinal hemorrhages were noted. Administration of large doses of **vitamin C** parenterally (1,000 to 15,000 mg.) prevented formation of new hemorrhages. The therapeutic requirements of these vitamins depend on the severity of the disease. As a general rule, the daily dosages range as follows: Thiamine, 5 to 10 mg.; riboflavin, 5 to 10 mg.; niacinamide, 50 to 200 mg.; pantothenic acid, 5 to 25(?) mg.; pyridoxine, 5 to 25(?) mg., and ascorbic acid, 500 to 1000 mg.

The value of diet regulation and controlled weight in pregnancy are discussed by Dieckmann, Turner, and Ruby.<sup>8</sup>

The pregnant patient must have a proper diet, but this does not mean that she should have an unlimited caloric

intake and as a result gain excessively in weight. The pregnant patient does not have to eat for two her own size. The diet must be increased during the last trimester.

Every patient whose total weight gain is over 10.9 kilograms does not necessarily have toxemia. Statistics do show, however, that the incidence of toxemia is increased in those patients who gain more than 13 kilograms. If the patient's weight is ideal before pregnancy, the authors believe that the maximum gain should be 7 to 8 kilograms. A procedure has been developed whereby it is possible to note the value and use of each food which composes a plan of daily food intake containing 1800 calories.

When the patient is not accustomed to drinking milk, recommendations may be made, as suggested by Turner<sup>9</sup> for "the use of milk in soups, desserts, or flavored beverages. However, the most inconspicuous and, in many cases, the most acceptable way in which to add milk is in the form of dried milk. Approximately 1½ ounces (5 tablespoons) of dried skim milk will equal one pint of fluid milk. This dried milk may be incorporated as a dry ingredient in the preparation of meat loaf, mashed potato, sandwich spreads, cooked cereals, hot breads, cookies, pastries, or puddings with little difficulty. Also, a palatable drink may be prepared by adding approximately 2½ tablespoons of dried milk to 1 glass (8 oz.) of fluid milk. This will provide approximately 15 gm. of high quality protein per glass."

Turner also pointed out that "milk contributes the major portion of calcium and phosphorus in the diet as well as a large share of the protein and vitamins of the B complex." While 2½ ounces of cottage cheese would be equivalent in protein content to 1 pint of milk, the cottage cheese would supply less than one tenth of the calcium, phosphorus,

TABLE I

APPROXIMATE EVALUATION OF DAILY PLAN OF FOOD INTAKE FOR PREGNANCY,  
CONTAINING 1800 CALORIES

Daily Food Intake	Quantity		Minerals		Vitamins					Foodstuffs			Calories
	Weight (Gm.)	Approximate Measure	Ca (Gm.)	Fe (Mg)	A (I.U.)	Ascorbic Acid (Mg)	Thiamine (Mg.)	Riboflavin (Mg)	Niacin (Mg)	Carb. (Gm.)	Pro. (Gm)	Fat (Gm.)	
Milk	960	1 quart	1.12	2.0	1,640	8	0.40	1.72	1.2	48	34	36	640
Egg	50	1 medium	0.03	1.4	495		0.07	0.18			6	6	80
Meat, poultry, or fish, cooked	100	Raw weight 4 oz.	0.01	3.3	2,807	2	0.28	0.37	5.9	1	24	13	215
Bread, whole grain or enriched	90	3 slices	0.03	2.0			0.24	0.13	2.6	45	9	3	240
Potato, cooked	100	½ cup	0.01	0.7	35	8	0.08	0.03	1.0	19	2		85
Green or yellow vegetable	100	1 serving	0.10	1.4	4,870	23	0.05	0.17	0.6	6	1		30
Other vegetable	200	2 servings	0.06	0.8	405	10	0.08	0.07	0.6	10	2		50
Legumes or beans: peas, navy, kidney, lima, or soybeans, or peanut butter	100 50 25	½ cup cooked ¼ cup 1½ table-spoons	0.03	2.4	20		0.14	0.06	1.8	19	7	3	130
Citrus fruit	200	1 cup juice											
Other fruits	100	1 serving											
Butter or enriched margarine	15	3 level tea-spoons			480	5	0.05	0.05	0.4	15	1	12	110
Coffee	25	2 table-spoons					0.04	0.01	2.3				
Sugar	15	1 table-spoon								15			60
Vitamin D concentrate													
Total			1.45	15.4	11,273	140	1.57	2.85	16.8	200	88	73	1,800

iron, vitamin A, thiamine, and riboflavin supplied by the milk. Two and one-half ounces of American cheddar cheese would supply calcium equivalent to one pint of milk but would be much lower in vitamins of the B complex. In this case, the further use of liver or other glandular meat one or two times a week would be desirable to augment the iron and A and B vitamins in the diet. Pork would enrich the thiamine intake. Eggs will supply a significant amount of vitamin A and iron. Legumes and whole grains will also contribute iron and vitamins of the B complex.

It is noted that the authors do not emphasize the addition of vitamins, calcium, and iron to the diet. Apparently this is not essential if their adequate diet plan is adhered to.

**Massive Nutritional Edema**—The incidence of protein deficiencies in pregnancy and the effect on mother and baby were studied in 400 patients by Arnell, Goldman, and Bertucci.<sup>10</sup>

The Food and Nutrition Board of the National Research Council recommends a daily allowance of at least 85 gm. of protein during the latter half of pregnancy and regards two thirds of the optimum level as a minimum subsistence level. Diets which fail to meet 50 per cent of the recommended optimum daily allowance, that is, diets containing less than 42.5 gm., are arbitrarily considered as deficient in protein content by the authors. Seventy-four patients fell into the deficiency group, their daily intake of protein being less than 0.75 gm. per kg. of body weight, as against a desirable intake of 1.5 gm. per kg.

The results which follow inadequate protein nutrition are neither so characteristic nor so dramatic as those which follow other types of malnutrition. Subclinical protein malnutrition, although exceedingly common, usually causes little

more than a slow and insidious wasting away of all the tissues, with associated weakness and general ill health.

A significant relationship was usually found to exist between the serum protein concentration of the blood at term and the protein content of the diet during the latter half of pregnancy. The average concentration was lowest in the deficiency group of patients. So-called idiopathic edema of demonstrable degree occurred in the deficiency group with a frequency (40 per cent) approximately four times greater than in the group whose daily protein intake was 70 gm. or more.

The authors feel that too much attention has been focused on obstetric complications and abnormalities as causes of maternal and fetal mortality, and too little attention paid to the general nutrition of the patient.

The average maternal gain in weight during pregnancy was greatest in the deficiency group. Some of the added weight can perhaps be explained by edema, but an analysis of the patients' food charts revealed a tendency, when the protein intake was low, toward high ingestion of carbohydrate and fat.

Because subclinical protein deficiency is common but clinical deficiency unusual, the authors present a detailed study of eleven patients admitted to the hospital in the last trimester of pregnancy because of massive edema of obscure etiology. The tentative diagnoses on admission included toxemia in six cases, heart disease in three, and nephrosis and anemia in one each. Further investigation showed the edema in all eleven cases to be due to a basic protein deficiency.

Edema was the only subjective or objective finding common to all cases. It had been present in mild degree for several weeks in all the patients, but the

massive degree appeared suddenly. Although it involved the lower extremities and trunk and, in some instances, the upper extremities and face also, it was usually the edema about the vulva of which the patients chiefly complained. In two instances there was a transient heavy trace of albumin, but otherwise all urinalyses were negative. The serum

All eleven patients were treated according to the following plan:

1. Complete bed rest.
2. Intravenous infusions of dextrose solution.
3. Vitamins B<sub>1</sub> and C were administered parenterally.
4. Puncture of the swollen labia, under strict aseptic precautions, was carried out in several cases in which swelling about the vulva was a source of great discomfort.

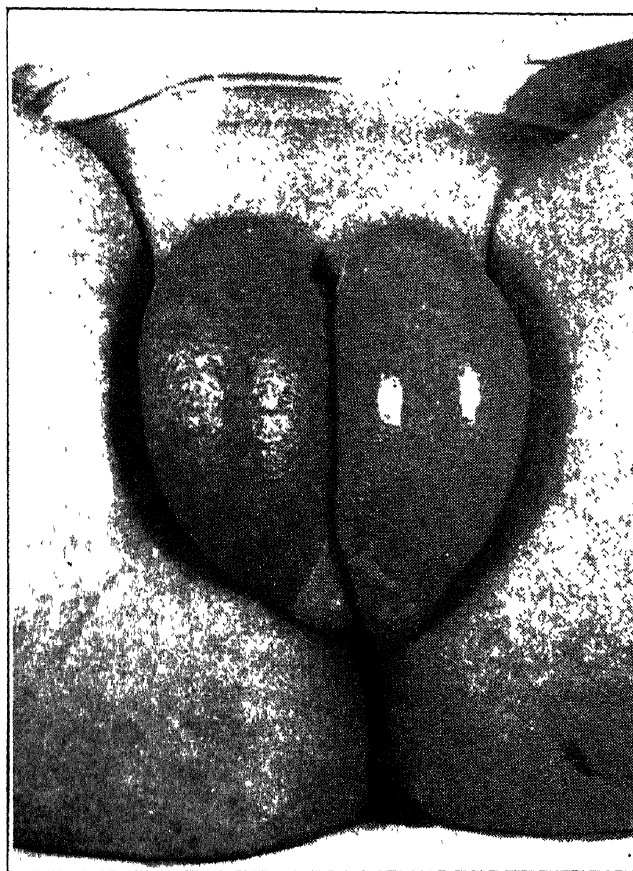


Fig. 1—Massive edema of the vulva in a case of nutritional edema in pregnancy before treatment. (Arnell, R. E., Goldman, D. W. and Bertucci, F. J.: J. A. M. A. 127: 1105 (Apr. 28) 1945.)

protein concentration of the blood was low in all eleven cases, the principal decrease being in the albumin fraction. In addition to the dietary protein deficiency, the hypoproteinemia was aggravated in seven of the eleven cases by conditions which resulted in either inadequate utilization or actual loss of the protein ingested.

5. A high-protein diet was instituted for all patients who did not have digestive disturbances which contraindicated oral feeding.

6. Transfusion of whole blood or of plasma. Whole blood is more desirable when treatment is first instituted, because of the anemia frequently associated with hypoproteinemia. After the anemia is corrected, plasma is more desirable, partly because there is no purpose to overloading the circulation with unneeded red blood cells and partly because a given amount

of plasma contains a much larger quantity of protein than does a similar amount of whole blood. Each of the eleven patients received an average of four transfusions, given in large quantities, at fairly close intervals, and totaling 2000 cc. Amino acids were used in three cases in this series.

The average duration of treatment in these eleven cases was fifteen days, and the average loss of weight 9 kg. (20 pounds), the range being from 7.4 to 19 kg. The edema which brought these eleven patients to the hospital has not reappeared in the periods from six months to five years, during which they have been followed up. Two of the group have been observed in subsequent pregnancies, both of which were normal in all respects.

### Mask of Pregnancy

The rôle of estrogen in physiologic hyperpigmentation was investigated by Davis<sup>11</sup> and his associates. In pregnancy, the increased amount of estrogenic substances present in the body predisposes to hyperpigmentation of the nipples, the areolas, and the linea alba as well as to the characteristic deposition of pigment on the face with the production of the typical "mask of pregnancy." The hyperpigmentation is always limited to areas naturally containing pigment. The hyperpigmentation observed in the young women treated with estrogens probably develops as a result of the establishment of a normal pituitary-gonadal relationship by the substitution of estrogens for the absent ovarian function. The authors suggest that a good pigmentary response in these young women is diagnostic of primary ovarian failure in the presence of a normal pituitary gland.

### Complications

**Cervical Pregnancy**—A report of two probable cases is offered by Studdi-

ford.<sup>12</sup> The author believes that cervical pregnancy is a definite, though rare, entity. Many cases may be unrecognized. Such pregnancies are rarely carried beyond the twentieth week of gestation. Usually it is necessary to intervene surgically before the fifth month because of hemorrhage, rupture of the amniotic sac, or perforation of the cervical wall. Profuse and violent hemorrhage accompanies the attempt to remove the placenta.

Enlargement and expansion of the cervix accompanied by bleeding in the early months of pregnancy, the detection of the corpus uteri surmounting the cervical mass should be regarded as suggestive of this condition.

Supravaginal rupture of the cervix should be treated by prompt and radical surgery. Intravaginal rupture of the cervix can sometimes be treated more conservatively; however, this complication may require cervical amputation or complete hysterectomy to control hemorrhage. When perforation is not present, in most instances the placenta can be evacuated; partially or completely, either manually or instrumentally, the hemorrhage can be controlled by packing.

**Syphilis** The present concept of syphilis in pregnancy is well summarized by Beerman and Ingraham.<sup>13</sup>

1. The mother, if not infected at the time of conception, may readily be inoculated *via* the uterine cavity. She is invariably infected, therefore, when her child is diseased.

2. The mother has positive blood serologic reactions for syphilis or some other evidence of the disease in almost every case in which the child is infected.

3. The fetus is infected in the later months of pregnancy and not close to the time of conception.

The authors believe this because: (a) Spontaneous abortion (prior to the fourth month of gestation) occurs with about

the same frequency among syphilitic and nonsyphilitic mothers. However, late miscarriage has a noticeably greater incidence among known syphilitic parents.

(b) Antepartum therapy for syphilis can assure the birth of a healthy infant in almost 100 per cent of cases, if it is continued throughout the later half of pregnancy only. (c) No embryo which contained spirochetes has been shown prior to the sixteenth week of fetal life. (d) Syphilitic skeletal changes have not been shown to occur prior to the sixth lunar month.

The taking of a single blood test at the time of the first prenatal visit will not uncover all syphilis in pregnancy. Syphilis may be acquired at the time of conception, or even in the later months of pregnancy. A repetition of this test at or near term is recommended.

The authors outline the principles of treatment of the syphilitic pregnant woman as follows:

1. Begin treatment of the syphilitic pregnant woman as soon as the diagnosis is established. A delay of even a few days may mean a syphilitic child.

2. To be effective the drug must be spirillicidal. Intravenous *neoarsphenamine* and *mapharsen* have been most thoroughly tried. *Penicillin* alone or in combination with these may rapidly supplant the older types of therapy.

3. Protection of the child is the primary aim of treatment during pregnancy. No treatment should be used which is likely to be injurious to either mother or fetus. If necessary the syphilis may be cured in the mother after delivery.

4. Treat largely with spirillicidal drugs during the late months. The fetus is seldom infected prior to the twentieth week. Treatment may be largely with heavy metal in the *arsenic-bismuth* regimen in the early months.

5. Reduce the initial dose of spirillicidal drug if treatment is begun after the fifth month. The first injection may be 0.2 gm. of neoarsphenamine (or its equivalent); the average dosage for the first three weeks should not exceed 0.3 gm. of neoarsphenamine per week. Total

weekly dosage need never exceed 0.45 gm. for the 150-pound adult.

6. Continuous alternating is preferred to concurrent treatment if arsenic-bismuth regimens are used.

7. After the fifth lunar month the length of the bismuth course should not exceed four to six weeks, lest infection of the fetus result from lack of spirillicide.

8. Treatment should be continuous; no rest interval.

9. Arsenical should be given for four to six weeks immediately before delivery.

10. If reactions occur, stop treatment and reevaluate. Do not injure the mother with overzealous applications of treatment for the unborn child. The average pregnant woman tolerates normal antisiphilitic therapy well but, should reactions occur, they may be serious and should not be considered lightly.

*Penicillin Regimen* — The therapeutic shock at the commencement of treatment in the pregnant woman with early syphilis may occasionally be harmful to the fetus. Reduction of the initial dosage is desirable for at least the first forty-eight hours. Specifically, if a 2.4 million unit total dosage were decided upon, the woman would then receive:

Ten thousand Oxford units sodium penicillin intramuscularly every three hours for eight doses, followed by 20,000 Oxford units sodium penicillin intramuscularly every three hours for eight doses, followed by 40,000 Oxford units sodium penicillin intramuscularly every three hours for fifty-four doses.

The total treatment course would occupy from eight to nine days. A negative blood serologic reaction for syphilis by the time of delivery is not essential to the birth of a healthy infant. In only seven instances, among the forty pregnant women in the authors' series who have thus far been carried through to term, was the mother's blood negative at the time of birth of her child. Thirty-eight per cent of the apparently healthy infants also had positive cord and neo-

natal Wassermanns. These uniformly reverted to negative in most instances by the age of three or four weeks, so that they apparently represented a transfer of syphilis reagin from mother to child rather than infection of the fetus.

The cord blood has little true diagnostic value, and cannot be depended on to decide whether or not the offspring of the syphilitic mother is infected. It may contain syphilis reagin and give a positive serologic test in the normal infant of a seropositive syphilitic mother; it may be negative even though the infant is diseased. This circumstance is equally true of the infant's blood during the neonatal period.

Results with the rapid treatment of early syphilis during pregnancy are reported by Speiser, Wexler, Thomas, and Asher.<sup>14</sup> Their technic follows:

The maximum dose of *mapharsen* given should be approximately 1 mg. per kilogram of body weight, and only one injection to be given a day. The average patient would then receive ten daily injections of about 0.06 gm. of *mapharsen*. To reinforce the treatment of this low dosage, four fevers induced by typhoid vaccine were included in the ten days. The fevers were given on the second, fourth, sixth, and eighth days. The first fever was induced with an initial injection of 0.1 cc. triple typhoid vaccine intravenously; the second with 0.2 cc.; the third with 0.4 cc., and the last with 0.6 cc. From two to three hours after the initial injection, another dose of equal amount was given in most cases. In general, a fever of at least 104° F. for about four hours was obtained. In addition, 0.1 gm. of *bismuth salicylate* in oil is given on the first, third, seventh, and tenth days of therapy.

Forty-three pregnant patients were treated for syphilis with massive *mapharsen* therapy. One death from arsenical encephalopathy occurred in this group. Of the thirty patients with early infectious syphilis who completed treatment and were kept under observation, good results from this therapy were obtained in a minimum of 76.6 per cent.

At the Bellevue Hospital prenatal syphilis clinic between 1936 and 1940, prior to the advent of massive arsenotherapy, there were thirty-four pregnant patients treated for early infectious syphilis with routine therapy. One death occurred from arsenical encephalopathy, five patients developed jaundice, and one exfoliative dermatitis. Only 50 per cent of the offspring were free from syphilis.

Intensive therapy proved safer and more effective than routine treatment. Nevertheless, there remains the risk of arsenical encephalopathy, and this is probably greater with intensive *mapharsen* therapy than when the same drug is employed in routine treatment.

**Otosclerosis**—Pregnancy complicated by otosclerosis was investigated by Allen.<sup>15</sup>

The author found that difficulties in hearing during pregnancy are frequently overlooked, neglected entirely, and often inadequately studied. A very careful family history concerning deafness should be taken on every pregnant woman who experiences appreciable changes in hearing. For progressive deafness to be considered as an indication for therapeutic abortion, a definite diagnosis of otosclerosis must first be made.

Otosclerosis should probably not contraindicate marriage or a trial pregnancy. Otosclerosis should not be considered as an indication for therapeutic abortion in the primipara. A familial history of deafness need not be present but may be one of the deciding factors in the decision for interruption of pregnancy. A multiparous woman may have considerable right to question the continuation of her pregnancy if accurate otological evidence obtained in previous pregnancies has shown a marked, sustained loss of hearing.

**Diabetes**—Observation of diabetic pregnancies by obstetricians and inter-



nists has revealed four salient abnormalities. These four abnormalities may be classified simply as first, maternal; second, obstetric; third, chemical, and fourth, fetal. Priscilla White<sup>16</sup> has attempted to evaluate these abnormalities as they occurred in a series of 181 con-

fifteen years. Today nephritis has replaced sepsis and is replacing coma as a cause of death of young diabetic patients. Ovarian failure is indicated by an increase in the serum level of follicle-stimulating hormone, by amenorrheas, and metrorrhagias.

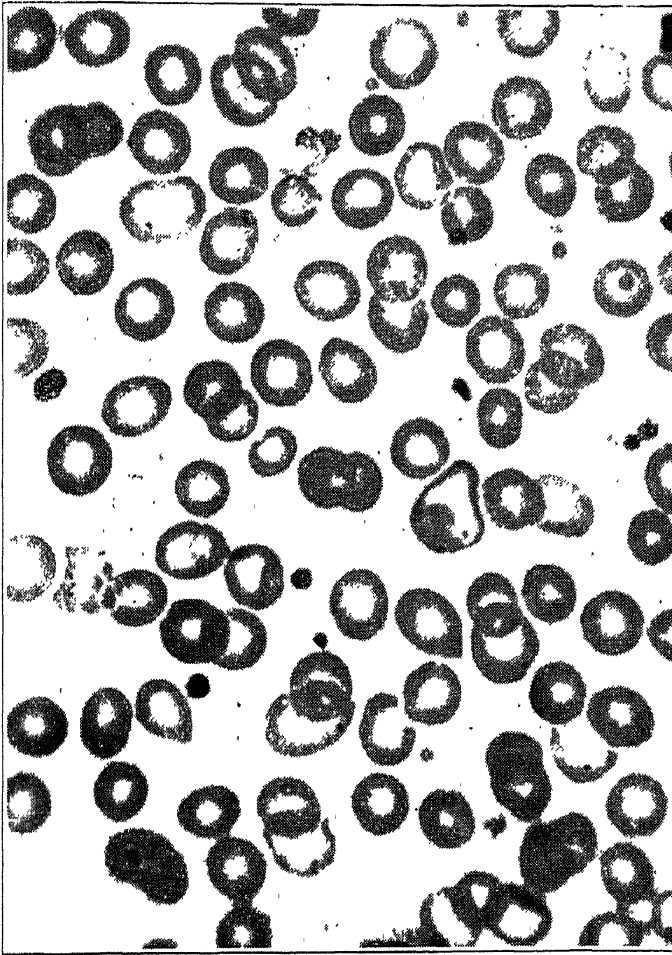


Fig. 2—Normal pregnancy: peripheral blood, showing the normocytic normochromic anemia. (Wolff, J. R. and Limarzi, L. P.: *J. A. M. A.* 128: 483 (June 16) 1945.)

secutive diabetic pregnancies studied between January, 1936, and June, 1944. In this series of cases, there were 1 maternal and 29 fetal deaths.

1. The prepregnancy abnormalities are two: Vascular disease and hypoovarianism. Vascular disease is almost inevitable in young diabetic patients in whom the duration of diabetes exceeds

2. The abnormal obstetric course of pregnant diabetic patients is well known. The striking abnormalities are five: The easy, early spontaneous interruption of the pregnancy occurring in at least 25 per cent of the cases, the high incidence of preeclamptic toxemia occurring in 36 per cent, breech presentation in 33 per cent, uterine inertia, common, and fail-

ure of lactation in nearly 100 per cent.

3. The chemical abnormalities which concern us here are (1) the low renal threshold for glucose; (2) water retention, and (3) the imbalance of the sex hormones of pregnancy. The low renal threshold for glucose, which is physiologic for pregnancy, complicates the dis-

hormones of pregnancy, fall of pregnandiol, and rise of chorionic gonadotropin occurred in 70 per cent of the 181 cases.

4. Fetal abnormalities are physical, chemical, and pathologic. A birth weight above the average for the period of gestation has been found in 80 per cent of the infants of diabetic mothers. The size

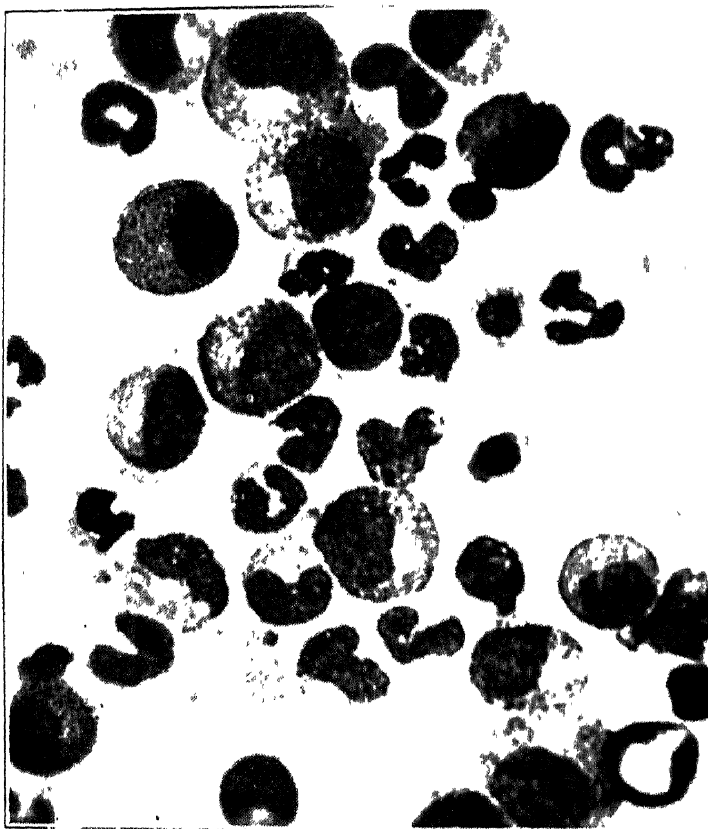


Fig. 3—Normal pregnancy: bone marrow, showing normal erythropoiesis and marked hyperplasia. (Wolff, J. R. and Limarzi, L. P.: *J. A. M. A.* 138: 166-169, 1947.)

ease diabetes. The loss of glucose in the urine may exceed 100 gm. per day, even with nearly normal levels of blood sugar. If uncorrected, this predisposes the patient to acidosis and, if overcorrected, to insulin hypoglycemia. Profound disturbance of water balance characterizes pregnancy in diabetic patients. This is shown clinically by the great gain in weight, visible maternal edema, hydramnios, and fetal edema. An imbalance of the sex

of the infant appears to be due to three distinct factors: obesity, edema, and splanchnomegaly, the liver, spleen, and heart being especially involved. The second physical abnormality is the high incidence of congenital defects usually involving tissue which is mesenchymatous in origin.

On the first postnatal day, respiratory, sugar, and temperature regulatory difficulties may be encountered, and forty-

eight hours after delivery the universal occurrence of jaundice.

The pathologic characteristics of the infants of diabetic mothers are almost diagnostic of maternal diabetes. They are enlargement of the liver, spleen, and heart, excessive hemopoiesis of the liver and spleen and islet hyperplasia.

dence of premature deliveries was zero, the incidence of toxemia of pregnancy, 2 per cent, and the fetal survival approached that of the nondiabetic pregnancies, 96 per cent. In contrast to this experience, in thirty-eight cases in which an abnormal hormonal balance was observed, premature delivery occurred in

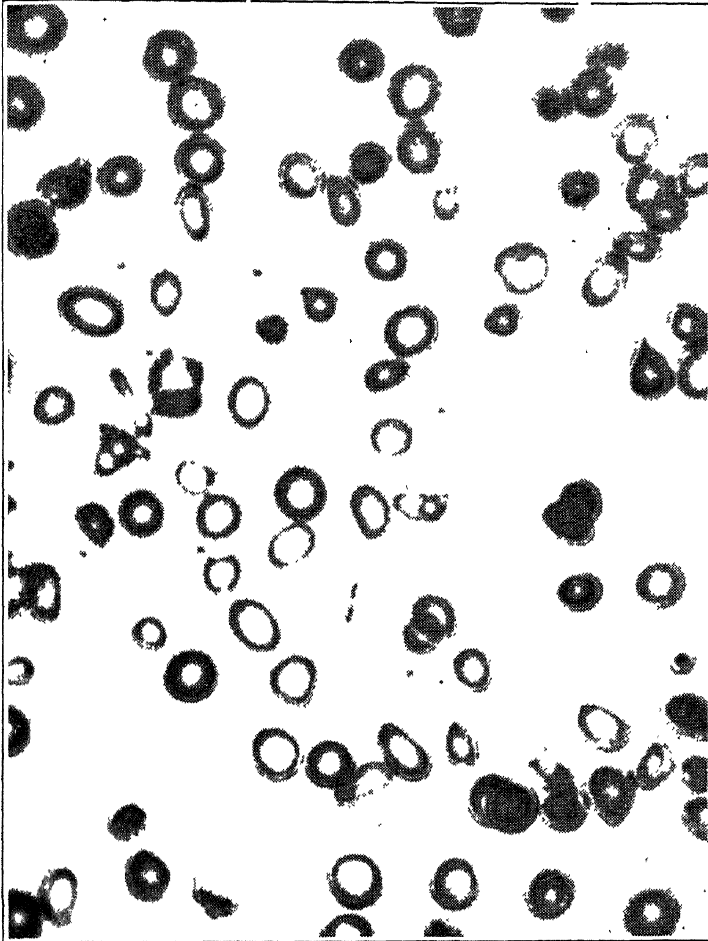


Fig. 4—Iron-deficiency anemia: peripheral blood, showing the microcytic hypochromic anemia.  
(Wolff, J. R. and Limarzi, L. P.: J. A. M. A. 128: 484 (June 16) 1945.)

In this series imbalance of the sex hormones of pregnancy appears to be the most important single harmful factor. In this series it is related to premature delivery, toxemia, disturbance of water balance and the abnormal fetus. Thus, when the hormonal balance was normal, as it was in 52 of the 181 cases, the inci-

40 per cent, preeclamptic toxemia occurred in 50 per cent, and the fetal survival was 50 per cent. Since the imbalance of the sex hormones of pregnancy occurred in abnormal clinical cases with poor fetal survival and the production of a characteristic fetus, an attempt was made in ninety-one cases to correct the

imbalance, to see if premature deliveries could be prevented, toxemias altered or averted, fetal survival raised, and a normal fetus produced. In the group so treated, the incidence of premature delivery fell to 15 per cent, preeclamptic toxemia appeared to be altered and prevented, and fetal survival rose to 90 per cent.

have been employed. Sodium chloride intake is restricted and, in abnormal cases, ammonium chloride is administered.

The delivery in the abnormal cases is premature, the time of choice being the latter part of the thirty-seventh or the early part of the thirty-eighth week. Cesarean section for this particular group is White's personal choice. The anes-

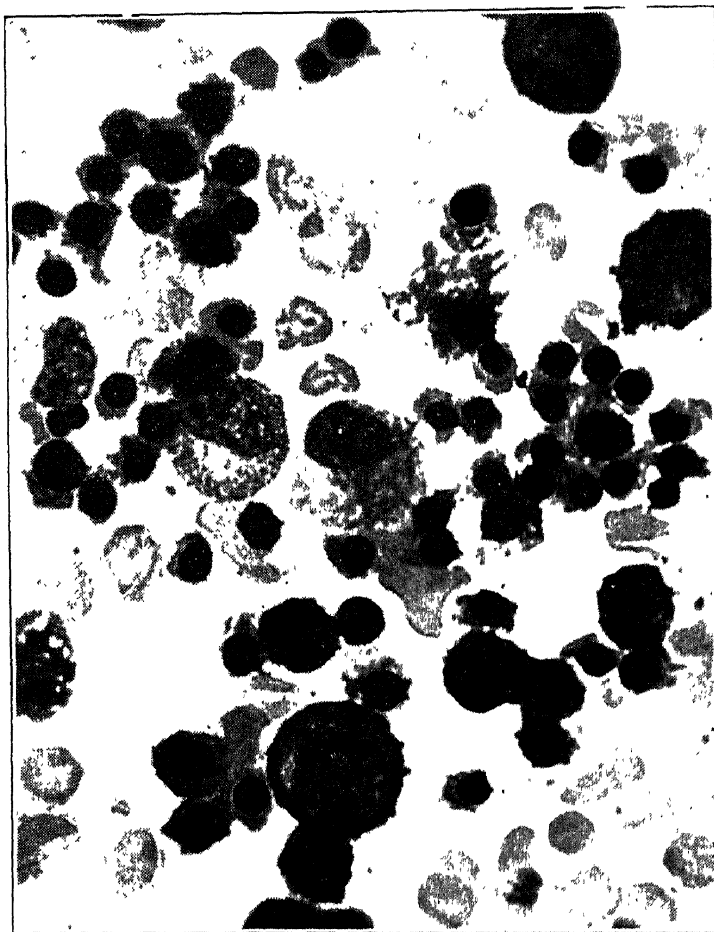


Fig. 5—Iron-deficiency anemia: bone marrow, showing the normoblastic hyperplasia. (Wolff, J. R. and Limarzi, L. P.: J. A. M. A. 128: 484 (June 16) 1945.)

The diabetic diet should be liberal in calories, 30 per kg. of actual body weight, high in protein, 2 gm. per kg. of body weight, and adequate in carbohydrate, up to 200 gm. daily, 150 for the mother and 50 for the fetus. Because of the low renal threshold, multiple small doses rather than a single large dose of insulin

thesis is spinal and sedation is prohibited. The best and most economical endocrine therapy to date is *diethylstilbestrol*, intramuscularly, and *progesterone*, intramuscularly. The average daily dose of each is 15 mg.

**Anemia**—A correlation of the peripheral blood and bone marrow findings

was made by Wolff and Limarzi.<sup>17</sup> Thirty patients were examined throughout pregnancy. These normal healthy pregnant women were first seen during the first six to ten weeks of pregnancy. At this time the peripheral blood and bone marrow were examined. The pe-

Peripheral blood and bone marrow analysis were also made on seventy-five other healthy women at various stages of their pregnancy.

The authors conclude that four types of bone marrow and peripheral blood patterns are observed during pregnancy:

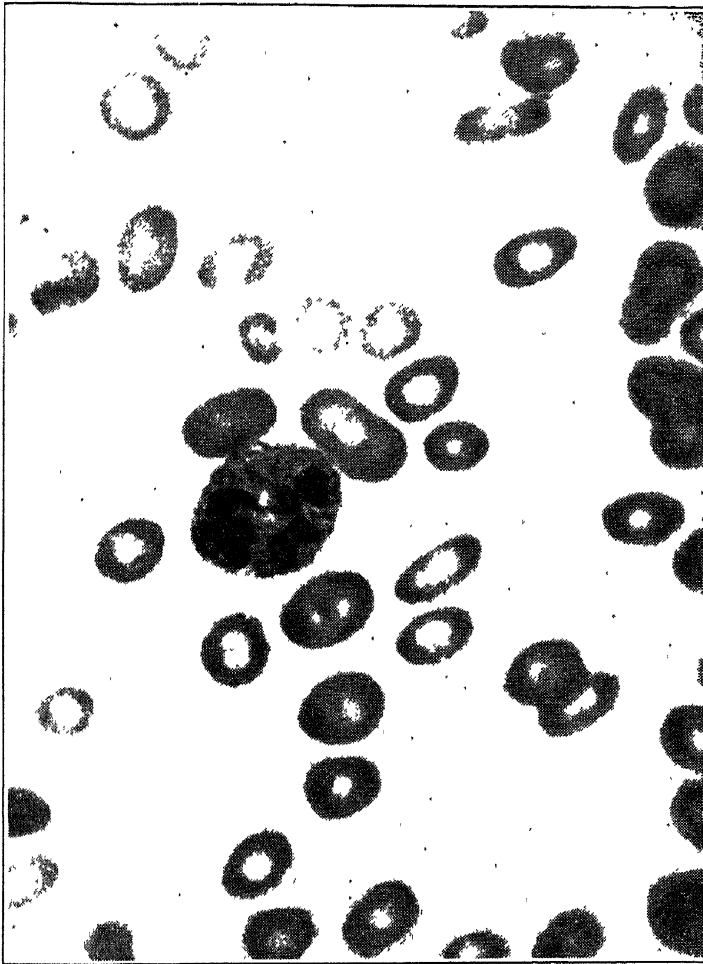


Fig. 6—Pernicious anemia of pregnancy: peripheral blood, showing a pernicious anemia neutrophil (macropolycyte). (Wolff, J. R. and Limarzi, L. P.: J. A. M. A. 128: 485 (June 16) 1945.)

ripheral blood was reexamined every four weeks until delivery, shortly after delivery, and at the six weeks' postpartum visit. The bone marrow was reexamined in many cases during the second and third trimester, in all cases shortly after delivery and in most cases at the final six weeks' postpartum visit.

1. A normocytic normochromic anemia in the peripheral blood. The bone marrow shows a normal erythroid pattern with a myeloid and megakaryocytic hyperplasia toward the end of pregnancy. The physiologic anemia is a normal state during pregnancy and is due to hydremia. Recovery is spontaneous dur-

ing the puerperium. No therapy is needed.

2. A microcytic hypochromic anemia with a normoblastic hyperplasia in the bone marrow. Adequate iron therapy corrects the bone marrow and the anemia. Occasionally, a mild microcytic normochromic anemia with a normal or

4. A megaloblastic type of bone marrow with either a macrocytic, normocytic, or microcytic and hypochromic peripheral blood pattern. Adequate liver therapy and supportive blood transfusions are needed to carry the patient through the pregnancy. Complete and permanent recovery usually follows. Atypical neutrophils



Fig. 7—Pernicious anemia of pregnancy: bone marrow, showing the megaloblastic type of erythropoiesis and abnormal granulopoiesis. Note the presence of a mitotic figure in one megaloblast. (Wolff, J. R. and Limarzi, L. P.: J. A. M. A. 128: 485 (June 16) 1945.)

normoblastic bone marrow is observed. No treatment is necessary as recovery follows delivery.

3. A macrocytic anemia with a normal or pronormoblastic bone marrow. Recovery follows delivery. Iron is indicated only when the mean corpuscular hemoglobin concentration is low.

(macropolycytes) in the peripheral blood are a diagnostic aid.

The most accurate method for the diagnosis and treatment of the true anemia of pregnancy is in the study of the sternal marrow. The changes in the peripheral blood are of a secondary nature and in many instances are misleading.

**Maternal Rubella**—Nine cases of congenital abnormality in the infant following an exanthem in the mother in the early weeks of pregnancy are reported by Albaugh.<sup>18</sup> It is suggested that the term "rubella" be used in place of German measles because the public has felt that German measles is a relatively innocuous disease.

Embryological data would indicate that the critical period for attack on the lens nucleus would be before the eighth week of pregnancy. This assumption is consistent with the reported statistics on disorder of the lens.

Greenthal<sup>19</sup> is of the opinion that every child should be allowed to contract rubella before maturity in spite of the danger of complications.

Available data would suggest that 100 per cent of the mothers who contract rubella in the first two months, and approximately 50 per cent of those who contract it during the third month, will give birth to infants with congenital anomalies.

The commonest lesions in the infants are cataracts, cardiac septal defects, and patent ductus arteriosus, deaf-mutism, and microcephaly. Nearly all of the infants are poorly developed and are feeding problems.

**Surgical Problems**—Surgical complications during pregnancy and labor are reviewed by Scott.<sup>20</sup>

I. *Fibroids and Frequency*—Conservatism is advised. Many of the smaller tumors are unrecognized during pregnancy. It is also a fact that the incidence of sterility is increased in women with fibroids. Their presence materially increases the incidence of abortion, miscarriage, premature labor, dystocia, and postpartum hemorrhage. Small tumors discovered during pregnancy are usually of little significance, and even large tumors may not seriously interfere. Size

alone may be an indication for myomectomy, and this is particularly true in the first pregnancy. In such cases, myomectomy done before complications have developed may result in a miscarriage but will leave a uterus capable of future pregnancies. All cases of degeneration of fibroids during pregnancy do not require surgical treatment, for the process frequently becomes quiescent under conservative management and the pregnancy may go to term. Torsion of a pedunculated tumor requires immediate operation.

In the series under study, there were fifty-one cases in which fibroids were discovered in pregnant women. Of these, seventeen required operation during pregnancy, three were dealt with at the time of labor, and thirty-one did not require treatment but only palliative measures.

II. *Ovarian Tumors and Pregnancy*—Ovarian tumors complicate pregnancy less frequently than do fibroids, but conservative measures play a smaller rôle in their treatment. The possibility of twisted pedicle is greater with the smaller sized tumors and, in those cases treated expectantly, this danger must always be kept in mind. Large ovarian tumors should always be removed because of the inevitability of distressing pressure symptoms as the uterus enlarges and because of the danger of complications such as pressure necrosis, hemorrhage into the tumor, interference with delivery, and malignancy. Borderline tumors, larger than a small grapefruit, are better removed, but, if possible, operation should be delayed until after the end of the third month. There were sixteen patients with ovarian tumors in this series. All of these patients were operated upon.

III. *Cancer of the Cervix Complicating Pregnancy*—During the past ten years, only four cases have been compli-

cated by pregnancy. If the pregnancy is near term, treatment can be delayed in the interests of the child, but in other cases the pregnancy should be terminated immediately after the diagnosis is made. Abdominal hysterotomy is the method of choice. The carcinoma is then treated by high voltage therapy followed by the use of radium.

IV. *Appendicitis*—Appendicitis is by far the commonest indication for an operation of necessity during pregnancy, although the incidence of the disease is probably no greater during pregnancy than at any other time. There seems to be little doubt that acute appendicitis during pregnancy is a somewhat more serious condition than in the nonpregnant patient, and the seriousness increases considerably when the uterus has risen above the pelvic brim.

There were forty-two pregnant patients sent to the hospital with a diagnosis of acute appendicitis. In twenty-one of these, the diagnosis was concurred in after admission, although in one patient a diagnosis of pyelitis of pregnancy at seven months was first made, and three days later it was necessary to do an emergency operation, when a gangrenous appendix was removed.

V. *Intestinal Obstruction*—Intestinal obstruction occurring during pregnancy presents many difficulties in diagnosis, and the delay in operation due to these may prove fatal. The obstruction is usually secondary to preexisting adhesions.

In this series there were seven cases of intestinal obstruction during pregnancy. Two were due to carcinoma of the sigmoid.

VI. *Hyperthyroidism During Pregnancy*—There were nine cases in this series in which the patients were admitted to the hospital with a diagnosis of hyperthyroidism during pregnancy. Of these, five diagnoses at the hospital

were simple colloid goiter, the symptoms being interpreted as the result of pregnancy. They were all treated expectantly, and all went to term. Three cases were true toxic goiters, one being an exophthalmic goiter, and the other two toxic adenomas. All three patients were operated upon and in no case did miscarriage occur.

In discussion, Falls stresses the value of *corpus luteum* extract injections as a prophylactic measure to avoid abortion in all of these surgical complications of pregnancy.

*Carcinoma of Cervix*—At the Cook County Hospital in Chicago, eight cases of carcinoma of the cervix that appeared in the past five years during a pregnancy were clinically studied by Kobak<sup>21</sup> and his associates. In seven patients, the malignancy was a stratified squamous cell carcinoma and in one, who died undelivered, it was an adenocarcinoma.

There is a tendency to regard carcinoma of the cervix during pregnancy as so improbable that other causes of bleeding are given stubborn precedence in diagnosis and therapy. The malignancy is thus diagnosed more often toward the end of pregnancy, when the growth has achieved large proportions. Carcinoma of the cervix continues to develop at a rapid pace during pregnancy. The earlier the diagnosis is established, the sooner effective therapy may be instituted, and the better the ultimate prognosis.

The treatment of these cases depends upon the disposition of the pregnancy. In the first trimester, the pregnancy is disregarded and deep *x-ray therapy* is instituted. With the death of the fetus, *radium* is added to the treatment. In advanced pregnancy, there is added concern for the cervix. The latter should be spared of the injuries that occur during parturition. If there is no infection as noted by the temperature or character



of the vaginal discharge, a classical *cesarean section* is performed to spare the cervix of trauma and to leave intact the fundal portion of the uterus to facilitate the radium therapy, which is started after uterine involution has occurred. A total of 4500 mg. hours of radium is given in three equally divided doses. As soon after the delivery of the baby as possible, deep x-ray treatments are started, and continued for a long period of time. In the presence of local infection, a Porro cesarean section is preferred. In pregnancies close to viability, the cesarean section may be deferred, and 1500 to 3000 mg. hours of radium may be given to the cervix to temporarily inhibit the progress of the new growth.

The ultimate prognosis for the patient hinges on the persistent continuation of the deep x-ray and radium therapy that is instituted after the disposition of the pregnancy.

**Nausea and Vomiting**—Eller and Randall<sup>22</sup> advise forced hydration for this condition. The following plan of treatment is advised by printed instructions given to patients:

Eat a fairly dry breakfast of toast and jelly, and a dish of dry cereal with a small amount of milk. Eat whatever you desire at other meals.

Between breakfast and lunch drink four glasses of water.

Between lunch and supper drink five glasses of water.

Between supper and bedtime drink six glasses of water.

This will not mean drinking a glass of water oftener than every half hour; you should be able to do this easily. Increasing the amounts toward the end of the day relieves you of drinking so much in the morning when your discomfort is apt to be worse. If you are most nauseated in the evening, reverse the schedule.

This program will necessitate your getting up in the night to urinate, but you will be doing this anyway; drink a glass of water each time you get up.

This treatment will seem difficult, especially if you have already started vomiting. If the

first few glasses are vomited, repeat them immediately and count only the glasses retained.

In a day or so you will find that your urine is almost colorless. This is the only way of being sure that you are drinking enough water. You may find that very hot or salt water is more easily retained.

You can be assured that as soon as your urine becomes clear, your nausea will improve and shortly will disappear altogether.

Sixty per cent of the sixty-eight patients treated were completely relieved of nausea within seven days; 47 per cent were relieved within four days.

There is evidence that the nausea of pregnancy follows and is due to the high serum concentration of chorionic gonadotropin in the first trimester of pregnancy; reduction of this concentration by diuresis may explain its effectiveness of this treatment.

**Toxemia**—A striking increase in the incidence of beriberi in Hong Kong during the years 1939, 1940, and 1941 and an almost parallel increase was observed in pregnancy toxemias, particularly eclampsia and preeclampsia, is reported by King and Ride,<sup>23</sup> the toxemia rate rising from 3.45 per cent during the preceding three years to 7.82 per cent. It was found that of 371 pregnant women with beriberi, 252 had pregnancy toxemia. The diagnosis of beriberi and pregnancy toxemia was supported by clinical and laboratory findings. Significantly high readings of the pyruvic acid content of the blood were obtained in the great majority of cases. In women with toxemia and beriberi, the prognosis was considerably more grave than in cases of toxemia without frank signs of beriberi. This was particularly seen in the eclampsia cases, in which a mortality rate at 38.8 per cent was found in thirty-six cases complicated by beriberi as opposed to 11.6 per cent in forty-three uncomplicated cases. It is suggested that the primary factor responsible for the

heavy increase in pregnancy toxemia during these years was vitamin B<sub>1</sub> deficiency.

**Preeclampsia—Effect of Prostigmine**—The influence of *neostigmine methylsulfate* on preeclamptic patients was studied by Woodbury<sup>24</sup> and his associates. Since studies indicate some antagonism between acetylcholine and pítressin, the question arose whether acetylcholine activity is altered or abnormal in eclamptic toxemia. There are some data which suggest that a relative decreased acetylcholine activity may occur in preeclampsia. The naturally occurring acetylcholine can be potentiated by inhibiting cholinesterase, the enzyme which destroys it. Neostigmine methylsulfate has this action.

Eight patients, pregnant seven to nine months, were studied. Five were diagnosed preeclamptic and showed edema, proteinuria, visual disturbances, and hypertension of recent origin. Two were hypertensive without evidence of any toxemias of pregnancy and one was a normal control. Cholinesterase activity was determined in placentas of eight normal and thirteen preeclamptic patients.

Individual susceptibility to neostigmine appeared to vary greatly. Pronounced effects were produced in one case with 0.25 mg. intramuscularly and 0.023 mg. intravenously, while in another case 1.0 mg. intramuscularly and 0.75 mg. intravenously was necessary to produce definite effects.

In the preeclamptic and the control patients, uterine activity and vascular effects appeared rather suddenly after a definite latent period of 90 to 120 minutes even after intravenous injections.

In all of the gravid patients it seemed to induce labor. In two of the patients in whom administrations were continued for twelve hours or longer, the uterus became hyperreactive and hypertonic, resulting in a prolonged labor. The ob-

servation that different preeclamptic patients may respond differently to moderate doses of neostigmine contributes additional support to the belief that there may be several different types of preeclampsia. The authors also found the cholinesterase activity of placentas from preeclamptic patients is greater than from normal patients.

**Eclampsia**—A seven-year review of eclampsia with special reference to treatment with *veratrum viride* is presented by Greene.<sup>25</sup>

*Veratrum viride* is an alkaloid, and is derived from the roots and rhizomes of hellebore. This plant is indigenous to both Europe and North America. The drug acts as a cardioinhibitor, vasodilator, and antipyretic. It is toxic in large doses and must be given carefully. Toxic reactions include sudden drop in blood pressure and pulse rate, nausea and vomiting, and eventually coma. Toxic reactions may be counteracted by gastric lavage or atropine in the usual dose. The preparation used was veratrone in doses of 0.3 to 0.6 cc. (3 to 10 minims), given by hypodermic injection.

Instructions for treatment of preeclampsia and eclampsia are as follows:

1. Give 0.3 to 0.6 cc. (5 to 10 minims) of *veratrum viride* immediately; repeat every fifteen minutes unless the pulse rate is below 60 or the blood pressure is below 120 systolic; thereafter, until the patient is conscious, repeat in 0.3 to 0.6 cc. doses if the pulse rate goes over 80 or the blood pressure over 150 systolic; after the patient is conscious and cooperative, give 0.3 to 0.6 cc. doses if the patient is nauseated or has severe headache, marked visual disturbances, or epigastric pain or convulsions.
2. Give 6 cc. of 50 per cent *magnesium sulfate* by deep injection immediately, 4 cc. every six hours for four doses, and then 4 cc. every twelve hours for four doses.
3. Give 500 cc. of 20 per cent *dextrose* intravenously at once; repeat every eight hours until consciousness returns.
4. *Catheterize* and give a soapsuds *enema* immediately.

5. Check the pulse and blood pressure hourly as long as coma persists, then every two to four hours while the patient is awake.

6. *Force fluids* (3500 cc. daily) by mouth as soon as possible.

7. Give no sedatives except for extreme restlessness or labor.

8. Institute a diet free of salt as soon as tolerated.

9. Measure the fluid intake and the urinary output; examine the urine daily for albumin.

From 1936 to 1941 before veratrum viride was used, the maternal mortality was thirty-five, or 26 per cent, and the infant mortality was forty-two, or 50 per cent. The following year there were fifteen cases of eclampsia. Fourteen of these cases received veratrum viride. All of them recovered.

The authors conclude that veratrum viride has a very definite place in the treatment of eclampsia.

The action of veratrone on blood pressure, urine volume, and urea clearance in the toxemias of pregnancy was studied by Willson.<sup>26</sup>

The effects of the administration of veratrone to patients with both pre-eclampsia and essential hypertension during pregnancy and after delivery were studied. The initial dosage varied from 0.5 to 0.75 cc. If, after thirty minutes, no change in blood pressure occurred, another injection, usually 0.25 cc., was given. The administration of the drug was followed by a decrease in pulse rate and a marked fall in blood pressure. This response was obtained more readily in the patients with pre-eclampsia than in those with essential hypertension. Coincidental with the fall in blood pressure, there occurred a diminution both in urine volume and in urea clearance which likewise was more marked in pre-eclampsia. The changes in kidney function are probably the combined result of the fall in blood pressure and an alteration in renal vascular dynamics.

### Mortality from Air Insufflation—

Death from air embolism following insufflation during pregnancy is reported by Breyfogle.<sup>27</sup>

The decedent, a housewife and trigravida, had consulted an osteopath because of an irritating vaginal discharge. The osteopath began to insufflate the vagina with silver picrate compound powder, 1 per cent silver picrate in kaolin (Wyeth), using a Shelanski insufflator (Wyeth) fitted with a soft rubber vaginal shield. It was estimated that from one half to two thirds of the standard container (Wyeth) attached to the insufflator was filled with silver picrate powder (2 to 3 gm.) when the treatment began. The patient was supine, with her feet elevated in stirrups, during the proceedings.

Approximately five minutes after the conclusion of the insufflation the patient sat up and asked a question. In a moment, she became noticeably pale and said, "I feel sick," and fell back on the examining table, suddenly inhaled deeply, and emitted a peculiar sound as if she was strangling. Shortly thereafter she was dyspneic, cyanotic, and unconscious, and a white froth began to exude from the mouth. The respirations were irregular and then ceased. Within a period of from twenty to thirty minutes after the initial symptoms appeared, no heart beat could be detected.

Although the exact port of entry was not demonstrated at autopsy, it may be supposed on the basis of the postmortem observations that air entered the systemic venous circulation at the site of placental implantation and was carried directly to the right auricle and ventricle of the heart.

The facts brought forth by studies of three other deaths resulting from vaginal insufflation during pregnancy indicate that it can be an extremely dangerous procedure, especially in the latter

half of gestation, and many near fatalities from this procedure have likely occurred.

**Placenta Previa**—A fervent plea for the conservative management of some varieties of placenta previa is made by Johnson.<sup>28</sup>

All cases of suspected placenta previa should be hospitalized for purposes of accurate diagnosis and for close observation of a developing anemia. Hospital rest may also decrease the bleeding episodes while awaiting good viability of the fetus.

When the pregnancy is terminated, either with the onset of labor or by pre-arrangement, it will, for purposes of treatment, fall into one of two groups, namely, those best delivered by cesarean section and those best delivered *per vaginam*. The first group includes all cases of central placenta previa and probably, in the interest of the baby, practically all previas in primiparas. This leaves for the second group those cases of partialis and marginalis occurring in multiparas. In the first group it is imperative only that the operator make sure that the operation is done at the safe time, *i. e.*, that the blood pressure be sufficiently high to withstand the sudden additional blood loss following separation of the placenta. Furthermore, the anesthetic should be as light and short as possible and the one which is least conducive to circulatory collapse.

The writer strongly advocates for the multipara the ultraconservative treatment as opposed to bagging, version, scalp traction, etc. It is helpful for one using it to have the earnest and positive conviction that untraumatized and unhurried previas do not bleed to death. Otherwise, a puddle of blood may cause one to change the treatment at the wrong time and with dire consequences.

The patient is taken to the delivery room and prepared and draped for delivery. This is not done with the idea that delivery or transfusion may be necessary, but because the delivery room is the cleanest and handiest place to rupture the membranes. With the utmost care, the middle finger of the left hand seeks a place near the edge of the placenta where the membranes alone separate the finger from the presenting fetal pole. Using the finger as a director, uterine dressing-forceps are passed to contact the membranes. Then, instead of puncturing them, the tips are used to bite a perforation. The forceps are inserted further and opened in order to produce a large rent. This allows the amniotic fluid to escape freely. The patient is returned to her room.

As labor progresses, the presenting pole aids in the dilation and acts as a natural tampon. In addition, the escape of the amniotic fluid decreases the intra-uterine volume and permits of at least a certain amount of retraction in the lower uterine segment. This may be a valuable aid in preventing blood loss. The labor is then watched with frequent checking of the blood loss, blood pressure, and fetal heart. Everything should be done to make the labor as comfortable and slow as possible. Plasma may be used to great advantage during the emergency, reserving the blood donor for the treatment of a possible postpartum hemorrhage or anemia.

The patient is returned to the delivery room at the end of the first stage of labor. At the completion of the second stage, which may end spontaneously or be assisted with outlet forceps delivery, the uterus may be gently supported, but no effort should be made to hasten separation of remaining attached placental tissue. This is especially true if free bleeding is present. There is no blood

escaping from unabrupted uteroplacental sinuses, and to provide a fresh source of bleeding may be the determining factor in the outcome. Allow the placenta to separate naturally.

The mother's blood picture must be the criterion for interruption of the pregnancy before the fetus has reached viability, and not an alarming history derived from a lay estimate of the amount of blood lost. The author concludes by requesting physicians to report to him any fatal case of placenta previa where there had been no cervical or intrauterine manipulation, or any attempt at manual removal of remaining placental tissue during the third stage of labor. He states that he had never heard of such a case. The maternal mortality for all types of delivery in the series reported (seventy-nine cases) was nil. The fetal mortality was average in cesarean section deliveries. It was low-est in conservative vaginal deliveries.

Williamson and Greely<sup>29</sup> describe their routine for the treatment of patients with vaginal bleeding in the last trimester of pregnancy as follows: Blood typing and cross matching is carried out. Unless forced to do so earlier by continued profuse vaginal bleeding, the patient is taken to the operating room on the fourth day following admission, where a sterile vaginal examination is carried out. If central placenta previa is found, cesarean section is the treatment of choice, while in the marginal as well as in some of the partial cases an attempt is made to control the bleeding by simple rupture of the membranes. However, the treatment for all types may be influenced by the parity of the patient, the duration of the pregnancy, the amount of bleeding, and the condition of the patient and the fetus. If the viability of the fetus is questionable, the cervix closed and firm, and there is little bleed-

ing, the patient may be returned to the delivery floor where she may continue to be observed for a much longer period. At the time of examination, the operating room has been prepared for immediate cesarean section or insertion of a hydrostatic bag, so that treatment may not be delayed should increased vaginal bleeding be encountered. If cesarean section is decided upon, the type of operation and the choice of anesthesia are dependent upon the preference of the operator.

A study of 162 patients with placenta previa is presented. While there was slight increase in the morbidity rate and an increase in the number of days, the patient remained in the hospital following cesarean section, the fetal mortality was greatly improved, and the delivery simplified by this procedure.

In discussion, Watson<sup>30</sup> feels that there are but two ways of treating the condition, simple rupture of the membranes or cesarean section. He believes the hydrostatic bag belongs to a past era in obstetrics. It did a good job in the days when cesarean section was a hazardous operation. In a ten-year study of placenta previa at the Sloane Hospital, he found, in contrasting cesarean section with bagging, in cases of central or of partial placenta previa, that the fetal mortality in cesarean section cases was 4.1 per cent and, in bagging cases, 50 per cent; that the maternal mortality in cesarean section was 3.4 per cent, and in bagging, 11.5 per cent; that the morbidity in bagging cases was 57.6 per cent, and in cesarean section, 37.9 per cent; and as regards the patients who had lost a great deal of blood and were in profound shock, he found in cesarean section 16.3 per cent, and, in the bagging cases, 61.5 per cent. There was a lower fetal mortality, a lower maternal mortality, less shock, and less hemorrhage in

the cesarean section cases than in those that had been bagged.

The fetal mortality with simple rupture of the membranes was 16.6 per cent as against 25 per cent with bagging. He found that shock and hemorrhage occurred not at all in cases of simple rupture of the membranes, and that 62.5 per cent of the patients were shocked when bags were used.

So with these two comparisons of the severe types of placenta previa, bagging *versus* cesarean section, there was no question but that section had the better showing; and in the milder marginal placenta previa cases, rupture of the membranes *versus* bagging, simple rupture was superior.

**Penicillin Transmitted Through Placenta**—The transmission of penicillin through the placenta was investigated by Hutter and Parks.<sup>31</sup>

Labors were closely observed in order to give an intramuscular injection of penicillin to each patient within a period of less than two hours before delivery. At the time of delivery, penicillin blood levels were obtained both from the antecubital vein of the mother and the umbilical vein of the infant.

The dosage was not effective until increased to a single 10 cc. intramuscular injection of 100,000 units of penicillin (10,000 units per cc.). With this dosage, observations were made on ten patients. Effective bacteriostatic levels were obtained in the fetal blood. The maternal levels ranged from 0.1 unit per cc. to 2.5 units per cc. The fetal blood levels ranged from 0.02 unit per cc. to 0.2 unit per cc.

The fact that penicillin passes from the maternal into the fetal circulation in effective concentrations suggests a wide therapeutic application of a relatively nontoxic agent for the control of penicil-

lin susceptible infections which affect the mother and her unborn infant. Of these infections, syphilis should receive greatest consideration. If penicillin will eradicate syphilitic infections in the mother and fetus, it should replace the much more toxic arsenical preparations in the treatment of syphilis in pregnancy. Penicillin, given during labor to patients with known gonococcal infections, should reduce the incidence of postpartum gonorrheal salpingitis and gonorrheal ophthalmia neonatorum. The prophylactic use of penicillin in patients with prolonged rupture of the membranes should reduce puerperal infection in the mother and increase fetal resistance to intra-uterine pneumonia.

**Penicillin in Rupture Membranes**—The transmission of penicillin to amniotic fluid and fetal blood in the human was investigated by Wolz and Zintel.<sup>32</sup>

The occurrence of infection of the uterine contents in patients with prolonged labor and in those with premature rupture of the membranes may constitute an indication for chemotherapy. In these circumstances, it may be desirable to use penicillin if this drug is proved to be transferred to the amniotic fluid and to the fetus. The present study was undertaken to determine the concentration of penicillin in the amniotic fluid and in the fetal blood after administration of the sodium salt of the drug to the mother by the intramuscular and intravenous routes.

The fact that adequate penicillin levels can be produced in the amniotic fluid as well as in the maternal and fetal circulations suggests the use of penicillin in the treatment of certain types of intra-uterine infection as well as its prophylactic use following premature rupture of the membranes and during prolonged labor.

**Heart Disease**—Estimation of the work of obstetric labor and its significance in heart disease were studied in thirty-nine patients by Sampson, Rose, and Quinn<sup>33</sup> by measurement of the oxygen consumption of the patient.

Complicated deliveries were accompanied by a persistent elevation of oxygen consumption presumably caused by an increased circulatory load. Five patients with rheumatic heart disease were studied. Two were free of symptoms and presented normal oxygen consumption curves; one had increased dyspnea and developed tachypnea, and a short period of very high rate of oxygen consumption during delivery; and one who was in heart failure at term maintained a high oxygen intake postpartum, and never regained her antepartum cardiac functional capacity. The fifth patient developed signs of serious failure during a prolonged first stage of labor and was uneventfully delivered by cesarean section with no consequential increase of oxygen intake.

The work of labor in both primiparous and multiparous women is the equivalent of mild to moderately heavy physical labor, the degree of which cannot always be predicted. In the presence of such a simple complication as a breech delivery, it may be increased markedly. This amount of physical work may be of the order that is commonly considered by clinicians as an unsafe risk for life or for maintenance of maximum function of cardiac patients in the ordinary routine of life. The authors feel that cesarean section, whereas presenting other risks, does not carry the dangers of this unpredictable load of physical work, although postpartum cardiac death is reported to occur after this procedure for reasons as yet undetermined.

## LABOR

### Placental Site—Effect on Fetal Position

The influence of placental site on fetal presentation was investigated by Torpin.<sup>34</sup> The great majority of placentas are located on the anterior or posterior wall of the uterus. The ratio found in this study was forty-seven anterior to fifty-three posterior. The placenta located on the anterior wall had a definite tendency to the production of occiput posterior presenting fetuses. Mathematically, when the placenta was anterior, the chance for occiput posterior presentation of the fetus was double what it was if the placenta was posterior, 33.3 per cent to 14.5 per cent. The placenta located on the posterior wall had an increased tendency to produce occiput anterior presentation in the fetuses. In this incidence, when the placenta was on the posterior wall, the chance of the presentation being occiput anterior was nearly twice what it was when the placenta was anterior, 59 per cent to 33.6 per cent. The incidence of occiput transverse presentation of the fetus in the first stage of labor was 26.5 per cent if the placenta was located on the posterior wall and 33 per cent if it was located on the anterior wall.

### Methergine in Third Stage of Labor

Clinical experience with methergine, a new synthetic ergonovinelike substance, is reported by Tritsch and Schneider.<sup>35</sup>

Methergine appeared to be nontoxic administered intramuscularly in 100 cases and intravenously in 100 cases. This drug appeared to reduce postpartum blood loss by both methods of administration as compared to other available statistics.

When given intravenously immediately after the birth of the infant, the drug

produced definitely less blood loss than when given intramuscularly immediately following placental delivery. By the intravenous route, immediately following delivery of the child, the placental delivery is accelerated by about three minutes. Incarceration occurred in the intravenous group in 3 per cent of the cases, but placental removal was easily accomplished under general anesthesia.

Methergine is being used experimentally for induction of labor. Farber (personal communication) has used it in over fifty patients and reports fair results.

### Placenta

A rectal maneuver for aseptic delivery of the placenta incarcerated in the lower birth canal is presented by Greenberg.<sup>86</sup> The maneuver consists of hooking the examining finger around the placenta and milking out the placenta by a stripping action of the anterior rectal wall.

This procedure is advocated only when complete uteroplacental separation has previously taken place, and when delay in placental delivery is due to one of the following: (a) Tight introitus; (b) placentovaginal disproportion; (c) atony of pelvic floor, or (d) spastic cervical segment due to previous administration of ergotrate, partially retaining the placenta. This method of placental removal is not advocated for routine management of the third stage.

Diagnostic rectal palpation in the third stage is recommended in cases of delayed placental delivery, because it is as informative as a vaginal examination without the associated risk of bacterial contamination.

**Manual Removal of the Placenta and Placenta Accreta**—An analysis of 217 cases of manual removal of the retained placentas following the delivery of a viable infant is reported by Aaberg

and Reid.<sup>37</sup> This operation was necessary once in every 210 deliveries. The gross mortality rate is 1.8 per cent. The gross morbidity rate is 28.8 per cent. The morbidity rate is markedly increased by the following factors:

- (a) A blood loss exceeding 500 cc.
- (b) A placenta allowed to remain in the uterus more than two hours following delivery.
- (c) The necessity for uterine tamponade.
- (d) Associated placenta accreta.

Placenta accreta occurred in 11 per cent of all cases. When the diagnosis of placenta accreta is made, irrespective of type, no further attempt should be made to remove the placenta pelvically, but an immediate supravaginal hysterectomy should be done. There is undoubtedly less risk to the patient who has a complete placenta accreta, because the operator probably will be unable to dislodge the placenta, and, therefore, will perform an immediate hysterectomy.

A definite plan of treatment, therefore, should be carried out in all cases of placental retention. Within one-half to one hour following delivery, a diagnosis of a retained placenta should be made. Preparations should ensue for immediate manual removal. This operation should be carried out in an operating room equipped for an immediate laparotomy, as well as for manual removal. After the patient is anesthetized, a **Credé expression** should always be tried. If this procedure fails, manual removal should immediately be attempted. Uterine packing should be resorted to if there is any question that the uterus is not contracting properly.

If a placenta accreta is encountered, the uterus should be packed at once with **sulfanilamide gauze** and an immediate supravaginal hysterectomy be performed. The pack is removed, vaginally, prior to amputation of the cervix. The amount of hemorrhage is markedly reduced by



this method. Usually, 10 gm. of *sulfanilamide powder* is placed under the peritoneal flap covering the cervical stump. Multiple transfusions are usually necessary when the blood loss has been great.

### Uterine Tetany

*Magnesium* has been graphically demonstrated by Abarbanel<sup>38</sup> to exert an immediate sedative effect upon the tetanically contracting human gravid uterus. Magnesium abolished tetany induced by the following oxytocic agents: Posterior pituitary hormone—whole extract (pitu-trin), purified oxytocic fraction (pito-cin), and purified vasopressor fraction (pitressin); quinine, ergonovine, and methergine (a synthetic ergonovinelike substance). Satisfactory results were obtained by the intravenous administration of either 2 cc. of 50 per cent solution of magnesium sulfate or 10 cc. of 20 per cent solution of magnesium gluconate. Magnesium probably acts directly on the myometrium, slowing the rate of the contraction wave.

Induced uterine tetany may be prevented by the prophylactic administration of intravenous magnesium salts from three to five minutes after administration of the oxytocic agent.

Clinical applications for the use of the antispasmodic properties of the magnesium ion have been found in the following conditions:

- A. Immediate relaxation of oxytocic-induced uterine tetany:
  1. During induction of labor or management of secondary degree uterine inertia.
  2. Third stage of labor for a separated but incarcerated placenta.
- B. Prevention of uterine tetany following use of oxytocics.
- C. Relief of afterpains.
- D. Alleviation of essential spasmodic dysmenorrhea.

E. Relaxation of Bandl's ring.

F. Relaxation of tetanically contracted uterus in abruptio placentae.

### Multiple Births

**Quadruplets**—Delivery of quadruplets by cesarean section under continuous spinal anesthesia is reported by Uillery,<sup>39</sup> of Philadelphia.

Mrs. K. C., white, aged 31, was delivered by cesarean section two years before, following a severe, rapid abruptio placentae. Despite immediate cesarean section the baby was stillborn, and the placenta separated with a large retro-placental clot and much infiltration of blood throughout the uterus, both tubes and ovaries, and extending out to the lateral pelvic walls. Her postpartum period was quite stormy and her temperature remained elevated from 104° to 106° F. for twelve days.

In this pregnancy the last menstrual period was March 12, 1944, with the expected date of confinement Dec. 19, 1944. During the first four months of the antepartum period there were considerable nausea and vomiting and it was necessary to hospitalize the patient for a week.

In August the uterus was found to be larger than normal for the duration of pregnancy, the fundus extending three fingerbreadths above the umbilicus, and x-ray examination revealed the presence of four fetuses (Fig. 8). She was immediately hospitalized and remained there until three weeks after her delivery. She was given a high *vitamin* diet and *progesterone* 5 mg. every other day, plus *iron* and extra vitamins. On October 24 she began to have some irregular uterine contractions and the uterus became quite tense. This continued for several days.

Accordingly, on November 1 an initial dose of 40 mg. of *procaine hydrochloride* was injected into the second lumbar interspace in 2 cc. of spinal fluid. A classic cesarean section was then performed. One placenta was on the anterior wall, and it was necessary to go through it to reach the babies. The first baby was delivered as a bilateral footling, the second also as a double footling, and the third as a vertex. These were all female babies and were enclosed in a single sac. The fourth infant was a male and was in a separate amnion with a small separate placenta.

The birth weights of the babies were 3 pounds 14 ounces (1758 gm.), 3 pounds 9 ounces (1616 gm.), 3 pounds 1 ounce (1389 gm.), and 2 pounds 14 ounces (1304 gm.). They all breathed and cried instantly on removal from the uterus and showed good muscle vigor. They were placed in separate incubators at once and kept there for one month.



Fig. 8—Appearance of four fetuses. (Ullery, J. C.: J. A. M. A. 128: 184 (May 19) 1945.)

### Cesarean Section

A comprehensive discussion of the cesarean section problem is offered by Dieckman.<sup>40</sup> The author lists as elective indications for cesarean the following:

1. **Tumors** (uterine or ovarian) blocking the pelvis should have been diagnosed before labor or early in labor.

2. **Contracted Pelvis**—*Cephalopelvic Disproportion*—The author's practice is to perform an elective cesarean if the true conjugate is less than 8.0 cm., or the transverse diameter of the outlet is less than 7 cm. with the baby estimated to weigh 3000 gm. or more. With the

true conjugate greater than 8 cm., the patient is given a test of labor. This means that the patient has hard uterine contractions at three- to five-minute intervals, lasting at least thirty-five seconds, for twelve to eighteen hours. The deadline is twenty-four hours of ruptured membranes or labor. In patients who are in labor for a longer period, delivery is effected vaginally, if necessary by craniotomy, or by cesarean hysterectomy.

3. **Repeat Cesarean Section**—During the past thirteen years, 1790 cesarean sections were performed and only one uterus with a cesarean scar ruptured with escape of the fetus into the abdominal cavity. In at least six more patients, when the bladder had been separated for a repeat cesarean section, there was found a complete separation of the scar.

Dieckman can find no evidence that the transverse incision of the lower segment is less likely to rupture. In view of the high maternal and fetal mortality due to uterine rupture and the impossibility of knowing which scars will not rupture, a previous cesarean section in general warrants a repeat operation. It should be performed seven to fourteen days before term.

4. **Placenta Previa** If rupture of the membranes does not control the bleeding, cesarean is indicated. If the insertion of a bag or Braxton Hicks version is required to control the hemorrhage, Watson's studies showed that 69 per cent of the cases required a serious operative delivery.

The author feels that diagnosis of placenta previa is by vaginal examinations. Visualization of the placenta by x-rays is not perfect or always feasible, nor does it give information as to the degree of previa.

5. **Breech presentations** in patients with contracted pelvis or in elderly pri-

mipara with large babies warrant elective cesarean section.

6. *Transverse presentations* in primipara and recurrent transverse presentations in multipara are frequently best treated by elective laparotrachelotomy.

7. *Heart Disease*—Patients who have fully recovered from cardiac decompensation during pregnancy are occasionally delivered by cesarean section at a time thought most opportune.

8. *Previous Operations*—Extensive vaginal or cervical plastic operations and previous radium application to the cervix frequently necessitate laparotrachelotomy.

9. *Fetal*—Elective cesarean section is justified in the interest of the baby in some patients, although it increases the risk for the mother (elderly primipara, previous sterility, low fertility, previous repeated stillbirths, fetal asphyxia in early labor).

Among the relative indications cited are:

1. *Large Fetus Postmaturity*—The incidence of postmaturity is approximately 7 per cent and of fetuses weighing over 4500 gm. is 1 per cent.

2. *Elderly Primipara*.

3. *Toxemia of Pregnancy*—Only the patient with the severe type of eclampsia and an uneffaced cervix should after eight to twelve hours of proper medical treatment be delivered by cesarean section.

4. *Abruptio Placentae*—The consensus of opinion is that patients presenting evidence of deep shock, low hemoglobin, rapid pulse, a uterus larger than the period of gestation; and one in which dilatation of the cervix does not occur after the membranes have been ruptured for six to twelve hours, are best treated by cesarean section.

Dieckman feels that the low cervical incision as a routine type for cesarean

section results in less morbidity and less mortality than any other type of cesarean section and should be practiced by anyone performing abdominal delivery after the thirty-fourth week of pregnancy with the possible exception of cases of placenta previa or where time is a factor. In these two latter conditions, if the case is not potentially infected, classical cesarean section with proper peritonization of the uterine incision (Schumann's modification) offers the best results.

Local anesthesia using one-half per cent novocaine is the safest anesthetic. Sixty per cent of operations are performed with it, and an additional 15 per cent are combined local anesthesia and inhalation.

If the obstetrician has no one capable of administering an inhalation anesthetic and he is not able to perform the operation under local anesthesia, spinal anesthesia, using 80 to 100 mg. of novocaine and preceded by one injection of 0.048 gm. ephedrine, should be used. Oxygen administration may be necessary for both spinal and caudal anesthesia until the fetus is delivered.

Laparotrachelotomy can be performed with a maximum maternal mortality of 0.2 per cent as an elective operation and 0.4 per cent after a test of labor (with these criteria).

Experience with 250 extraperitoneal cesarean sections is recorded by Waters<sup>41</sup> with detailed description of the anatomy and technic involved. Whereas previous operators attempted in a supravescical extraperitoneal operation to "peel" the peritoneum from the bladder and pelvic fascia, an almost impossible undertaking, in Waters' operation the peritoneofascial flap was "lifted" and dissected as a unit, a perfectly feasible and not too difficult surgical procedure. Therein lies the difference between success or failure in a rather old procedure, and it is the

only modern major contribution to the technic that he has made, states Waters.

Because of the comparative newness of the operation, 1939, the technic described by Waters is given in detail.

The vaginal orifice and tract are thoroughly antiseptized and a careful and complete vaginal examination made. The fetal head, if fixed, is pushed well upward to facilitate its later extraction. An indwelling catheter is inserted into the bladder, and tested for free inflow and outflow. It is connected to an irrigator containing a sterile solution of water colored with methylene blue. Prior to abdominal incision, the bladder is filled with 150 to 200 cc. of solution, or enough to obtain moderate distention. This is maintained until bladder dissection is well advanced.

The abdominal incision is a left lower rectus from pubes to two thirds of the umbilicus. The pyramidalis is separated from the lower end of the rectus muscle. Or Pfannenstiel's incision, which is satisfactory, may be chosen.

After retracting the rectus muscle laterally, the already distended bladder may be seen through the overlying transversalis and perivesical fasciae. The relatively thin transversalis fascia, with some thickened transverse trabeculae, is incised vertically. A "T"-shaped incision is made in the perivesical fascia in the following manner: A one-inch vertical incision is made through the laminated fascia covering the distended bladder down to its muscularis, at a point about two thirds of the distance up on the exposed bladder. The Bard-Parker knife handle is inserted downward between bladder fascia and muscularis, the tissue freed, and the fascia then divided vertically with a Mayo scissors. This permits the filled bladder to herniate forward. (The vesical vessels lie between fascia and muscularis, and serve to orient the operator.) The cross of the T-incision in the fascia, which must be generous, is made by insinuating curved Mayo scissors between bladder fascia and muscle and dissecting as in a cystocele operation, cutting after visualizing. The fascia, though laminated, is easily separable as a unit with knife handle and Mayo scissors. Laterally it fans out and thins where it contains enmeshed fat tissue. At the urachus it is adherent, and when a large exposure is needed, the urachus must be "surrounded" by dissection, doubly tied and cut, lest the peritoneum be torn there.

The peritoneofascial (P. F.) flap or fold is now lifted upward by Mayo scissors and knife-handle dissection, keeping close to the bladder muscle. The dissection proceeds over the top and left upper corner of the bladder, seeking the most accessible portion of the uterovesical fold of peritoneum.

It is best to empty the bladder at this stage. The P. F. flap and bladder are now drawn apart, using gauze, until the uterovesical plica is identified lying against the lower segment. (The lower segment is now being viewed through the posterior portion of the fascial envelope of the bladder and the uterine fascia over the lower segment.)

An incision is made below the hernial sac-like fold of uterovesical peritoneum and through the fascial layers noted, down to the glistening muscularis of the lower segment. The finger is inserted then beneath these fasciae, and the fascia and bladder are stripped and freed from the front of the lower uterine segment. (This is comparable to the procedure, in lower segment transperitoneal cesareans, whereby the bladder is freed from the lower uterine segment.)

Obviously, to expose a large lower extra-peritoneal segment it is now necessary to cut through the posterior portion of the perivesical fascia still attached to the bladder, starting with the initial opening below the hernial plica. This is done by knife dissection, using the handle to push the bladder muscularis away. This permits visualization of the intact P. F. fold before cutting the fascia close to the bladder, whereupon the P. F. fold is completely freed of attachment and lifted upward from the bladder. The bladder is dropped below the pubis and retracted with a Fritsch retractor. Lateral fascial retraction is obtained with one and one-half inch Richardson retractors.

A centrally placed transverse "nick" is made in the exposed uterine segment one and one-half inches above the depth of the bladder effacement, down to membranes. Cultures are taken from amniotic sac (and later, after removing the fetus, from the cervical segment). With a bandage scissors placed in the "nick," a crescentic incision is carried in either direction, first to left, then right, the ends reaching a level about one and one-half inches above the "nick." The size of the baby's head determines to a degree the acuteness of the curve. The ends always avoid the broad ligaments. No attempt is made to control any uterine wall

bleeding until the baby has been removed from the uterus.

In vertex presentations, one blade of a forceps is passed in laterally, then swung below the disengaged head and used as a vectis to pry and lift out the head, with strong fundal counterpressure being exerted to facilitate delivery. It is best first to turn the head so that the occiput presents in the wound and birth is by extension. Breech deliveries are simple, and internal versions may be performed. The baby is removed, and the edges of the wound grasped with T-clamps, using one at each end and one in the center of each crescent. *Ergotrate* is given intravenously and the placenta and membranes are immediately extracted manually.

Two layers of No. 1 chromic single sutures are placed in the uterus. The first is a running stitch, beginning at the left end of the incision, with stitches placed accurately and closely. The second layer is a Cushing continuous stitch, completely inverting the first. In the event of uterine wound infection, discharge into the cervical segment and lochia is effected. This suture also produces direct uterine fascial approximation, a most important factor in sound uterine wall healing.

The operative area is dried and No. 0000 chromic ties placed on any bleeding points. "*Sulfa*" powder is sprinkled (not packed) over the retrovesical tissues and a Penrose rubber tissue drain placed in the retrovesical space and brought out of the lower end of the wound. The peritoneofascial flap is replaced over the bladder from whence it was lifted by dissection. Fine, interrupted sutures reapproximate the left rectus to the median raphe. The rectus fascia is sutured with continuous No. 1 chromic catgut and the abdominal wall closed with silk or Michel clips.

To briefly review the manner of fascial incisions, it is seen that first the thin transversalis fascia is incised. Then the perivesical fascia is divided as it covers the fundal portion of the bladder near the parietovesical peritoneal reflection. After separation of this, especially over the left upper bladder angle, the same layer is again incised posteriorly to expose the fascia covering the lower uterine segment. Thus the bladder is "denuded of a fascial skullcap," which remains attached to the peritoneum, from bladder fundus to the uterovesical pouch. This permits the peritoneum to be freely and easily lifted and the bladder dropped below the symphysis behind a Fritsch retractor. Transverse incision of uterine fascia over the

lower segment increases the mobility of the uterine peritoneum. The rest of the operation is essentially a laparotrachelotomy with (Kerr) transverse crescentic incision through the lower uterine segment. The drain is left in two to five days, depending upon the infectivity of the case. The catheter is left in two days to rest the bladder.

The total cesarean incidence is 2.67 per cent. Of 1837 cesareans in this twelve-year period, 23.4 per cent were of some extraperitoneal type. Our experience in the 431 extraperitoneal sections, including 250 of the supravescical type, demonstrates such a low mortality that they almost never use a Porro operation, do a craniotomy on a living child, or hesitate to use it where they believe an intrauterine infection is probable or even remotely possible. The indication should be any potentially infected case.

Employing the technic described in this paper, there were four bladder perforations in the 250 extraperitoneal sections. There were no persisting fistulas, since all perforations are easy to see and repair. All but two of the sixty-eight peritoneal punctures were recognized and repaired before the uterus was incised. In other words, in only two cases was there peritoneal cavity communication with an infected operating field.

Two hundred and forty-one of the 250 extraperitoneal cases here reported were given either spinal anesthesia alone (190) or spinal with some terminal anesthesia. Waters believes it to be one of the safest anesthetics for cesarean section.

**Extraperitoneal Cesarean**—A peritoneal staining technic for extraperitoneal cesarean section is reported by Bourgeois<sup>42</sup> on a series of ten patients with excellent results. The technic is as follows:

After preparation of the vagina and sterile vaginal examination, the urinary bladder is emptied by catheter and refilled with about 250 cc. of 0.0001 per cent *phenolsulfophthalein* solution. The catheter is left in the bladder. A midline incision is made down to the transversalis fascia which is stripped by blunt dissection from the undersurface of the recti muscles. A small opening is then made into the peritoneal cavity at the extreme upper pole of the incision. Through this opening a soft rubber catheter, to which a syringe containing 5 cc. of 0.5 per cent aqueous *methylene*

*blue* solution has been attached, is inserted into the peritoneal cavity toward the bladder. Any free peritoneal fluid is aspirated. The bladder is then emptied and the dye injected over its peritoneal surface. Injection is performed slowly with simultaneous manipulation of the catheter tip through the transversalis fascia and peritoneum to bring the dye in contact with all of the future peritoneofascial flap, using this procedure the edges of the peritoneal opening are elevated by an assistant to prevent overflow of dye onto extraperitoneal tissues. When injection is completed the catheter is withdrawn. The peritoneum is then closed transversely with a continuous suture of fine chromic gut and the transversalis fascia longitudinally with a continuous suture of the same material. Occasionally the tissues involved will accept only one layer of suture. The resulting sharply demarcated blue peritoneum guides subsequent dissection of the peritoneal flap.

The peritoneal cavity was accidentally entered three times, once because of undue traction on the peritoneofascial flap, twice because the flap was incompletely stained. Incomplete staining of the peritoneofascial flap occurred in the first instance because the amount of dye was insufficient; in the second because injection of the dye was performed in the presence of a distended bladder. There was no injury to bladder or ureters.

### Rupture of the Uterus

Rupture of the uterus, as reported by Lynch,<sup>43</sup> has occurred at the Boston City Hospital forty-four times in the last twenty-five years. During this period, there have been 41,706 deliveries, which is an incidence of 1 in 1118.

Of the nontraumatic factors, the one which contributes by far the greatest number is the rupture following a previous cesarean section. In this group the number of cases was eleven, amounting to 25 per cent of the total.

The maternal mortality in this series of cases was 52 per cent and the fetal mortality, 89 per cent.

The treatment of choice is a *supravaginal* or *complete hysterectomy*, depending on whether the cervix has or has not been involved and the prob-

able amount of sepsis present. If rupture has occurred and the baby is still in the uterus, it is important that it be not extracted from below because of the practical certainty of extending the rupture, aggravating the bleeding, and contributing further to the shock.

Rarely, if the rupture takes place in the first pregnancy with the loss of the baby and the patient is extremely desirous of having a child, the tear in the uterus may be sutured and the organ retained. This, however, should be restricted to uteri in which the torn edges are not too irregular or too badly traumatized and where the question of sepsis is not too prominent. All women in whom a ruptured uterus has been repaired should, of course, have a subsequent pregnancy terminated by a cesarean section.

In discussion, Vogt<sup>44</sup> notes in one institution four ruptured uteri of 15,498 deliveries, an incidence of 1 to 3874 cases. There were two cases of rupture of the uterus following the classical cesarean section, in both of which the rupture was found at the site of the original uterine wound. Supravaginal hysterectomy was done in both instances with the death of one mother and both children. There were two cases of rupture following version and extraction.

Whitacre<sup>45</sup> cited forty four cases of rupture of the pregnant uterus from the Peiping Union Medical College, China, occurring between the years 1934 and 1941, a hospital incidence of one in ninety-five cases. Thirty eight of these forty-four patients were seen for the first time as emergencies.

The most important causes of rupture of the uterus in this series were contracted pelvis and transverse presentation of the fetus, which accounted for about 50 per cent of these accidents.

When applicable, they repaired the tear in the lower uterine segment and cervix first and then did a supravaginal hysterectomy. Removal of the cervix is not urgent and it is often better not to extend the operation by including it. Finally, a tube is passed through the

The entire mortality occurred in ruptures of the lower uterine segment. This is partly because of the relative difficulty of recognizing these cases as ruptures, as compared to the somewhat dramatic and clear-cut syndrome represented by bursting of the corporeal segment.

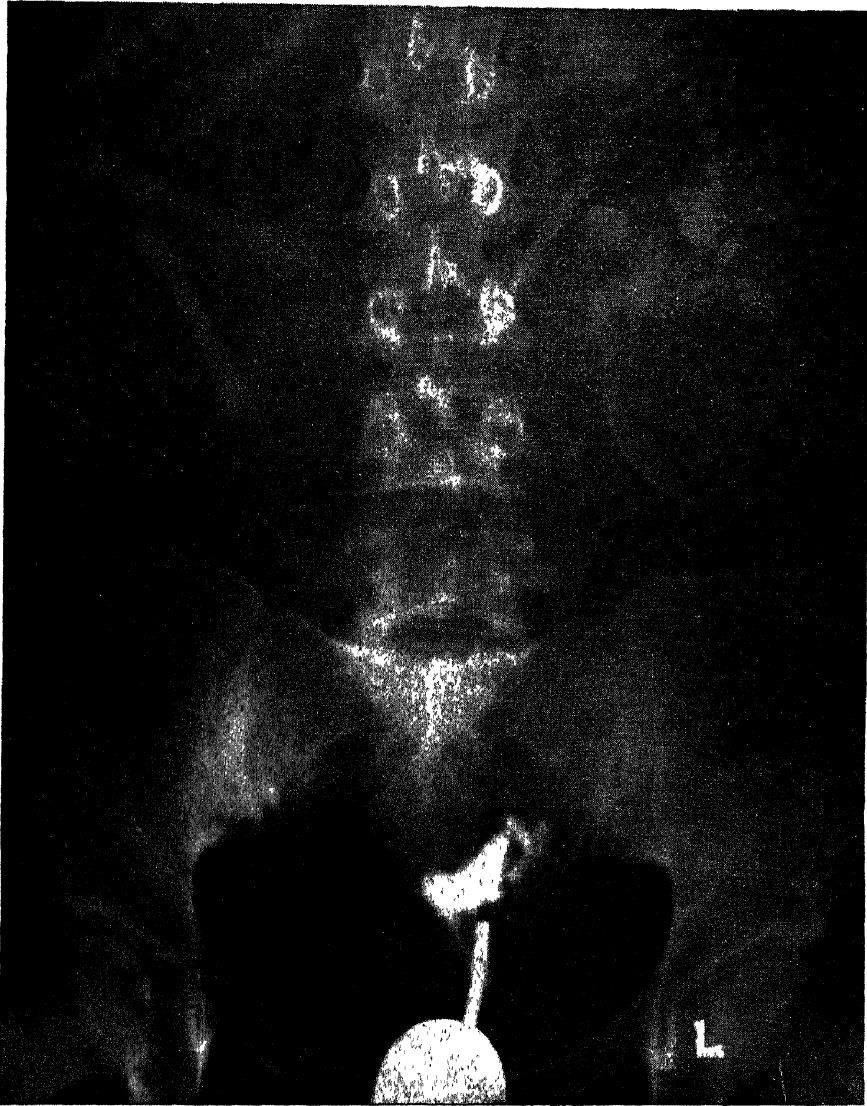


Fig. 9—Five cubic centimeters lipiodol. Dye beginning to pass out tear in left side of uterus. (Sheffery, J. B.: *Am. J. Obst. & Gynec.* 49:423 (Mar.) 1945.)

*cul-de-sac* into the vagina to provide dependent drainage.

Cosgrove<sup>46</sup> found thirty-two ruptures in a series of almost 67,000 live births. Twenty-one mothers recovered and eleven died, a mortality of 34 per cent.

Eastman,<sup>47</sup> among some 53,000 deliveries at Johns Hopkins, had a total of 53 ruptures of the uterus, an incidence of 1 in 1000. Among the 17 cases of spontaneous rupture, the average age of the patients was 36.3, and the average

parity, 6.4. All of the patients were multiparas.

Prophylaxis seems to be most important. Following rupture, early diagnosis is imperative.

Hysterosalpinography as a diagnostic aid in certain types of ruptured uteri is advocated by Sheffery.<sup>48</sup>

Rupture of the uterus can occasionally be almost symptomless. Fractional injection of a dye (lipiodol) can give aid in the diagnosis of these cases.

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## ANALGESIA

### Paracervical Anesthesia

Paracervical anesthesia for the relief of labor pains is reported by Rosenfeld.<sup>49</sup> In this form of anesthesia, the local anesthetic is injected alongside the cervix, the aim being to anesthetize and thus block the sensory nerve fibers in the parametrium. This is easily accomplished by a bilateral injection of the anesthetic solution parallel to and alongside the cervix to a depth of from 3 to 4 cm. into the lateral fornices.

One can readily and easily inject the patient by himself, relying on the sense of touch. The materials required are a 10-cc. syringe, a long flexible needle, and the anesthetic solution.

After the patient has been washed with soap and water and sprayed with merthiolate solution, she is draped. An Asepto syringe full of aqueous *merthiolate* is injected into the vagina. The author usually begins by injecting the left side first. The index and middle fingers of the left hand are pressed into the space between the left side of the cervix and the vaginal vault, and the needle is guided so that it pierces the vault close to and parallel to the cervix. This procedure is then repeated on the right side.

In an effort to secure more prolonged anesthetic action than was obtained with *novocaine*, resort was made to *nupercaine*. Solutions of 1:2000, 1:1500, and 1:1000 were all used with very satisfactory results. *Eucupin* was employed with equally satisfactory results. This series consisted of 100 patients, of whom 45 were nulliparas and 55 multiparas. Sixty-nine per cent of the multiparas and 22 per cent of the nulliparas delivered spontaneously.

The author compares the method with *caudal* anesthesia. Caudal enjoys certain advantages over paracervical. When continuous caudal is used, there is, of course, no need for reinjection. When using the paracervical approach, reinjection is necessary when pains reappear if one desires to have the labor continue painlessly. Should operative procedures become necessary to terminate labor, one can proceed without delay when using caudal, whereas, with paracervical, additional anesthetic procedures, *e. g.*, local infiltration, pudendal block, inhalation, or spinal, are necessary. Caudal has another advantage in that, when it is successful, the perineal stage is painless. With the paracervical method, the level of anesthesia is higher than the perineum, and as a result the perineal stage is usually painful. However, in the last few cases in this series, infiltration of the vaginal wall and posterior vagina have succeeded in securing a practically painless perineal stage. In the average multipara, the perineal stage lasts only a very short time, and the pain can easily be controlled by either local infiltration of the perineum or a few whiffs of either nitrous oxide or ether administered during the course of the pain.

The author concludes that solutions of procaine, nupercaine, and eucupin, with and without the addition of adrenalin, are effective. The relief afforded



when these drugs are injected paracervically is much more prompt and pronounced than when drugs are used which act on the central nervous system. Nupercaine and eucupin induce anesthesia which lasts much longer than that obtained with procaine.

### Spinal and Caudal Anesthesia

A comparison of the value and applicability of caudal and spinal anesthesia in obstetric practice is presented by Montgomery<sup>50</sup> and his associates.

They present 470 cases in which spinal anesthesia was undertaken for vaginal or abdominal delivery. There were 3 failures to enter and 467 successful introductions (99.3 per cent). The anesthetic agent chosen was *pontocaine*, administered in a moderately weighted solution of 10 per cent *dextrose* and *physiologic salt solution*, which had a combined specific gravity of 1.020 in contrast to the usual 1.006 to 1.008 of human spinal fluid.

Anesthesia was administered in the lateral position with the head elevated on a firm pillow. The back was prepared with soap and water, ether, and an antiseptic tincture. Local anesthesia was placed in the skin and muscle and a 22-gauge needle was introduced at the third lumbar interspace. Only enough spinal fluid was withdrawn to identify the position of the needle point certainly and the 3.1 cc. of anesthetic mixture was injected at moderate pressure in five to six seconds. The needle was then promptly withdrawn, the patient turned upon her back, and the head of the table elevated 10° in a reverse Trendelenburg position, the head of the patient being raised still further with a firm pillow.

Anesthesia was administered to multiparous patients when the pains were vigorous, the head engaged, and the cervix dilated at least two thirds. In

primigravidas, the spinal anesthetic was given when the cervix was completely dilated and the head was on the pelvic floor, or at least a plus 2 station.

Because of the increased tone of the uterus, the spinal anesthetic method should be reserved for spontaneous delivery, forceps extraction, or cesarean section. It is a most undesirable agent in breech extraction and version where, of course, uterine relaxation is essential. A fall in systolic blood pressure of 20 mm. or more was noted in forty-six patients (10 per cent). *Ephedrine* was administered prophylactically to many of the cesarean section cases.

Moderate to severe postpartum bleeding was encountered in forty-two deliveries (9 per cent) and uterine packing was inserted in nineteen.

There were no maternal deaths and no cases which approached a critical condition as a result of anesthesia. Of the fetal deaths, one occurred during the delivery itself and might conceivably have been a result of anesthesia, for the blood pressure at one time fell to 70/50.

The authors then review their findings in caudal anesthesia. The procedure was attempted in fifty-six cases and successfully introduced in forty-seven. In the vast majority, they employed the apparatus, needles, 1½ per cent solution of *metycaine*, and technic advocated by Hingson and Edwards.

Eighty per cent of the patients had quite satisfactory relief during labor, but in 48 per cent of the total group supplemental anesthesia of one kind or another was necessary during delivery. In five patients (11.8 per cent), there was at one time or another a drop of 20 mm. or more in systolic pressure. No postpartum hemorrhage was noted, and the bleeding after delivery was in general the least observed with any form of anesthesia.

In a comparison of the value and applicability of caudal and spinal anesthesia, the authors believe that spinal anesthesia can be more readily and certainly administered, with less "fuss" and great promptness. One is impressed in both caudal and spinal anesthesia by the salutary effect upon the baby—the freedom from anoxemia, the promptness of cry, and the early establishment of normal respiration. Caudal anesthesia produces more profound relaxation of the perineal and pelvic floor muscles than the spinal. Under caudal anesthesia, the fetal head arrests in the low mid- or deep pelvis, not infrequently in a transverse or posterior position.

The same criticism may be leveled at spinal anesthesia if the administration is made too early, particularly in a primigravida patient. In fact, the dangers are greater, for not only will the head fail to descend farther after the anesthesia is given, but also there is less relaxation of the pelvic floor and perineum to compensate for the high level of a forceps delivery. The spinal method should, therefore, be withheld in a normal primigravida until the descent phase is completed, the scalp is visible, and a true outlet forceps delivery can be performed.

Both methods require vigilant observation by a physician or a nurse trained in anesthesia. Their ultimate place in obstetric practice is not yet indicated.

### Continuous Caudal Analgesia

In a study of 500 consecutive cases managed with continuous caudal analgesia, Nicodemus<sup>51</sup> notes that labors are longer. Uterine contractions are of less intensity, the expulsive force of the abdominal musculature is lost. Occiput posterior positions rotate less often, and operative deliveries are increased. The advantages of this technic are easier

and safer breech deliveries, a lower incidence of stillbirths, a lower maternal morbidity, diminished blood loss with delivery, less permanent damage to the birth canal, and a pleasant, happy, co-operative patient.

In discussion, Hingson<sup>52</sup> states that Nicodemus did not indicate the upper level of analgesia in those cases in which he attributed the prolonged labor to caudal analgesia. His observations have been that the forces of labor are impaired and eventually made ineffectual in prolonged high caudal blocks above the segmental levels of thoracic eight. Ideally, caudal block should not extend above the umbilicus (T-10). Nevertheless, on some occasions, unexpected high caudal block results from the average dosage of 30 cc.

Montgomery,<sup>53</sup> in discussion, states that aside from the technical difficulties, and the complications of minor or moderate severity, the crux of the situation seems to lie in the problem of how far we can go with any method of anesthesia in obstetrics which inhibits the natural powers of labor. Certainly, thus far, no satisfactory substitute has been found for the natural fashion of delivery, including the dilatation of the cervix by recurrent contractions of the uterus in the first stage, and propulsion of the fetus through the birth canal by the combined efforts of the uterus and abdominal muscles in the second stage.

Now, with the advent of caudal anesthesia and of spinal anesthesia in obstetrics, we rather impertinently apply our forceps with the head in midpelvis, or in low pelvis, and complete in a few minutes what Nature ordinarily takes an hour or two to accomplish.

The regional methods of anesthesia, that is, spinal, caudal, and local, offer many advantages over central or systemic anesthesia. The injection of a local

anesthetic agent in the perineum during the final stage of delivery and for the repair of episiotomy, combined with "whiffs" of nitrous oxide and oxygen or ether, is one of the very safest of anesthetic methods.

### Single Block Caudal Analgesia

Distinct advantages in favor of caudal analgesia given in repeated single blocks as contrasted with continuous caudal are cited by Hanley and Malone<sup>54</sup> in a series of 152 cases.

The large majority of multiparas are carried through labor and delivery with a single injection of 25 cc. of  $\frac{1}{4}$  per cent *tetracaine* with 0.18 cc. (3 minims) of 1:1000 *adrenalin*. In those cases where a repeat caudal is necessary, because the patient again feels pain, she is prepared, and given a second injection, the usual amount being 20 cc. If a third injection is given, the amount is also 20 cc. When the presenting part is on the perineum, the patient is placed on the delivery table and given a last caudal block of 25 to 30 cc. of 2 per cent *procaine* as the authors have found that subsequent injections of tetracaine give less complete and shorter periods of analgesia.

The average number of caudal blocks that it was necessary to give in this series was less than three. Therefore, the authors feel it more advantageous to give one, two, or three single caudal blocks for complete analgesia and delivery than to use the continuous caudal. The patient can move at will with single caudal block. The chances for infection are much less with single caudal block. The chances for broken needles are much less.

The chances for massive subdural injections are much less with single caudals. The authors never insert the needle deeper than is necessary to enter the caudal canal, while in the continuous

setup the needle must be inserted to the hub in every case. With the needle in place for several hours and the patient moving about, perforation of the dura or blood vessel could easily occur, with a serious accident resulting on subsequent injections. It is much easier technically to insert an ordinary steel spinal needle into the caudal canal than the malleable ones used in the continuous caudal.

One-sided analgesia is very seldom seen with repeated single caudal blocks. The patient can lie flat on her back or turn as she wills. On the other hand, with continuous caudal, the patient may have a level of anesthesia on the dependent side with continuous cramps on the upper side.

**Effect on Uterine Motility**—Frankel<sup>55</sup> studied the labors of fifty patients under caudal analgesia by means of the Lorand tocograph, an instrument devised for recording graphically the contractions of the uterus through the anterior abdominal wall. He found that the most important factor affecting uterine motility was the level to which the analgesia ascended. When the recommended level (between the sixth and tenth thoracic segments) was maintained, only 20 per cent showed a decrease in uterine motility, and these were minor changes. The remainder were unaffected. When the level of analgesia was permitted to ascend above the fourth thoracic segment, labor was interrupted in 69 per cent of the patients. When a low level of analgesia involving only the sacral nerves was achieved in two patients there was a great improvement in the strength and frequency of the uterine contractions.

### Hospital vs. Home Deliveries

Bakwin<sup>56</sup> questions whether indiscriminate hospitalization for delivery has

had a favorable influence on either maternal or neonatal mortality. There is material for thought in the report of the Frontier Nursing Service of Kentucky. The service has reported a maternal mortality of 0.75 per 1000 births in its first 4000 deliveries, as compared with 5.6 for the white population of the United States of the same time. These deliveries were done in homes which were extremely poor. Operative deliveries were rare, and stillbirth and neonatal death rates did not differ significantly from those of the country as a whole.

Bakwin believes that hospitals are unsuited for the care of the newborn. The obstetric nurseries are crowded and expose the infants to epidemics, particularly those of diarrhea. Pneumonia, sepsis, and other infections are not infrequent. These conditions are rare in the home. Recent studies suggest that the separation of mother and baby, as practiced in hospitals is unnatural and unphysiologic. The system of bringing babies to their mothers only at fixed intervals and allowing them to remain for limited periods, he argues, is not conducive to proper breast feeding, especially during the first three weeks of life. Bakwin readily agrees that the hospital is the proper place for the delivery of selected patients when difficulties are anticipated, but he feels that some modification of the present system of indiscriminate delivery in hospitals should be made.

### Puerperium

Again the advisability of getting the obstetrical patient out of bed a few days after delivery is debated. Rosenblum, Melinkoff, and Fist<sup>57</sup> report from the Cedars of Lebanon Hospital in Los Angeles that beginning with March, 1944, 106 delivered women, unselected in any

manner, were made ambulatory on the third or fourth postpartum days. These women, the "intermediate risers," were given the privilege of going to the bathroom, which was always in the room, instead of using the bedpans. In addition, they could eat their meals out of bed if desired, leave the bed to bathe, and remain up while the bed linen was being changed. However, the rest of the time they were asked to remain in bed. Thus, the time actually spent in bed must have amounted to 95 per cent of the total time. The routine as regards postpartum care was otherwise not changed.

An unselected series of women was made ambulatory during their first or second postpartum day. This group, comprising 247 patients, is called the "early risers." Aside from early ambulation, there were no changes made in the management of these patients. Patients delivered by cesarean section were included in this series without selection. The third group comprised 229 patients kept in bed more than five days.

The contention that early puerperal rising may cause excessive bleeding is disproved by the statistics, which actually show less frequent abnormal bleeding in the early group than in the late group, the intermediate group being approximately the same. Involution of the uterus was uniformly good in all groups.

The feat that early rising would cause a breakdown of episiotomy or abdominal wound incisions is likewise unfounded, only one instance of perineal skin separation occurring in the entire series, and this in a patient in the late rising group.

The claim advanced by some obstetricians that early rising may cause later prolapsus and retroversions is also disproved. Of early risers examined at one month and at six weeks, 28.7 per cent had either a midposition or retroversion of the uterus, while 34.6 per cent of the

intermediate and 24.4 per cent of the late risers had the same positions—relatively similar totals. This indicates that early rising causes no significant alteration in the position of the uterus, at least within a period of four to six weeks following delivery.

Data compiled indicate that delivered women can safely and advantageously get up early in the puerperium with no harmful results occurring. Bowel function particularly is improved as a result of early rising in the puerperium. Early puerperal rising reduces the amount of nursing care required.

The statistics show no particular advantage to third or fourth day puerperal rising as compared to the earlier first and second day figures. It is the authors' opinion that early rising results in more rapid and comfortable convalescence, with less asthenia and less postoperative and postpartum depression.

### Puerperal Infection

The methods employed in the Obstetrical Department of Jefferson Medical College Hospital in the treatment of puerperal infection are outlined by Hinebaugh<sup>58</sup> in the light of specific chemotherapy.

The following manifestations of this infection are discussed:

1. **Endometritis** (Sapremia) — The present method of treatment is dependent upon a bacteriologic diagnosis in addition to the clinical findings. This may be determined by lochial or uterine culture.

A uterine culture is taken as follows: The patient is placed on a bedpan and the external genitalia are carefully cleansed with lysol solution or other suitable antiseptic. Using sterile gloves and instruments, the physician gently inserts a bivalve speculum into the vagina, exposing the cervix. All lochial discharge

is wiped away from the exposed cervix and vaginal fornices. A sterile glass pipette with suction bulb attached is then carried into the uterine cavity, care being taken not to allow the pipette to brush the vaginal mucous membrane, thus causing contamination. The material thus obtained is immediately cultured for both aerobes and anaerobes. The value of anaerobic culture cannot be emphasized too strongly for the anaerobic streptococcus is frequently found as a causative agent, and the recovery of *Clostridium welchii* is by no means rare. A laboratory report is requested at the end of twenty-four hours to avoid delay in the institution of treatment.

The plan of specific therapy is dependent upon the type and number of organisms recovered in the culture. Of these, *Streptococcus pyogenes* is most common. **Penicillin** is the best therapeutic agent when infection is due to the staphylococcus, *Streptococcus pyogenes*, *Streptococcus haemolyticus*, *Streptococcus anaerobius*, gonococcus and *Clostridium welchii*. The dosage and method of administration are dependent upon the type and severity of the infection. The primary object in every case is to bring the infection under control as quickly as possible. The plan adopted by the author is as follows: Injections are given intramuscularly, the initial dose being 20,000 units. Subsequent doses of 10,000 units each are administered every three hours, making a total of 90,000 units during each twenty-four-hour period. Treatment is continued until the temperature has remained normal for forty-eight hours. The penicillin is then stopped and the patient's subsequent course carefully followed. In all infections caused by the *Streptococcus haemolyticus*, the initial injection is given intravenously.

Penicillin is contraindicated because it is ineffective if infection is due to *E. coli*,

*B. proteus*, *B. pyocyaneus*, or Friedländer's bacillus. In all cases in which infection is due to these gram-negative bacteria, *sulfonamides* are used. The author has *sulfadiazine* to be most effective and it is generally well tolerated by the patient. It is administered orally, the initial dose being 2 gm. followed by 1 gm. every four hours. The drug is discontinued after the temperature has returned to normal. An alkali, such as *sodium bicarbonate*, 0.972 gm. (15 grains), is administered with each dose of sulfadiazine. Blood levels of 8 to 12 mg. are suggested for optimum results. These determinations are advised every forty-eight hours. Frequent blood counts should be made in view of the tendency of the drug to cause anemia and leukopenia. The urine is examined daily for the appearance of sulfadiazine crystals or any evidence of renal damage. Should this or any other toxic manifestation occur during the course of treatment, the drug is stopped immediately.

In addition, Hinebaugh urges *transfusion* of all patients whose hemoglobin is below 70 per cent and erythrocytes less than 3,500,000. Generally repeated small transfusions (250 cc. of whole citrated blood every second day) are more effective than one or two large transfusions. In addition, the patient is given large amounts of *vitamin B* complex, *vitamin C*, *liver extract*, and *iron*.

II. *Metritis*—The management of this type of infection is essentially the same as for endometritis. The organisms most frequently encountered are the hemolytic streptococcus and the staphylococcus against which *penicillin* is particularly effective. An initial dose of 20,000 units is administered intravenously followed by 10,000 units intramuscularly every two hours or a total of 130,000 units during each twenty-four hours.

III. *Pelvic Cellulitis* (Parametritis)—The following plan has been adopted: At the earliest sign of infection, a cervical culture is made in the hope of determining the causative organism. In most instances, it is found to be *Streptococcus pyogenes*. *Penicillin* therapy is immediately instituted. If the infection is of moderate severity, the dosage and administration are the same as that for the treatment of metritis. If, on the other hand, the degree of intoxication is profound, an initial dose of 20,000 units is administered intravenously followed by constant intravenous injection of penicillin in normal saline. The drip is so regulated that 3000 units are delivered every hour. If the causative agent is found to be penicillin resistant, *sulfadiazine* is given. In order to establish a satisfactory blood level rapidly, 5 gm. of the *sodium salt* is injected slowly intravenously; this is followed by the oral administration of 1 gm. every three or four hours. In cases in which the infection is of a mixed type, a combination of penicillin and sulfadiazine may be used. The patient is carefully observed for any evidence of abscess formation.

The author has found the use of *x-ray* of definite value in the treatment of this condition and employs it as an adjunct to specific therapy and surgery. Although the exact mode of beneficial effect is not known, it has materially helped to limit and subsequently localize the infection. It also tends to hasten healing following incision and drainage. Small doses are used, 25 to 75 roentgens per treatment, the total dose not to exceed 500 roentgens.

IV. *Pelvic Peritonitis* (Perimetritis)—Under the present plan of management, the patient is placed in Fowler position. This affords postural drainage and tends to prevent ascension of the in-

fection. Vomiting is controlled and decompression accomplished by either the *Wangensteen apparatus* or a *Miller-Abbott tube*. The passage of gas per rectum is facilitated by the insertion of a *rectal tube*. Enemas should not be given. *Fluid intake* is maintained by intravenous drip, 1500 to 3000 cc. daily of 5 per cent glucose in normal saline. *Blood transfusions* are routinely administered to combat anemia and increase the patient's resistance. The predominant organisms which cause puerperal peritonitis are susceptible to *penicillin*. It is administered by the intravenous route previously described under the treatment of severe pelvic cellulitis. Because of the severity of the infection, the dosage requirement is higher. In addition to the 20,000-unit initial dose, the intravenous drip is regulated to deliver 5000 units during each hour. *Sulfadiazine* may be used in conjunction with penicillin because of the inhibiting effect on the colon bacillus which is frequently found as a secondary invader. *X-ray* therapy has proved to be of definite value in the treatment of these cases.

V. *Bacteremia* (Septicemia)—*Penicillin* is by far the best therapeutic agent and should be given intravenously. Repeated small *blood transfusions* are equally as important as specific therapy.

VI. *Thrombophlebitis*—Infection of the veins with thrombus formation may occur as a result of severe trauma during delivery or in association with local infection. Frequently the infection begins in the uterus as a local thrombophlebitis, then extends by way of the pelvic veins through the common iliacs either upward into the vena cava or downward through the external iliac into the femoral veins.

*Paravertebral nerve block* is the treatment of choice. The rationale for this plan is based upon the concept that

vasospasm which results from afferent impulses arising in the injured vein segment was primarily responsible for the development of thrombophlebitis. When this procedure was carried out, the relief of pain was prompt and the disappearance of edema rapid. Thus the duration of the infection was materially shortened. *Heparin* has also been used with considerable success. The use of this drug, however, is not without danger. At the present time, the author advocates continuous caudal or continuous spinal anesthesia of three hours or longer. Its superiority over paravertebral nerve block is due to the marked vasodilatation which occurs and is maintained for the duration of the anesthesia. Relief of pain is immediate, and usually within five to ten minutes vasodilatation of the extremities is manifested by marked warmth and redness. In most instances, edema disappears within twenty-four hours, the temperature returns to normal, and the patient is allowed out of bed at the end of seventy-two hours.

VII. *Infected Abortion*—The radical plan of management is based upon the concept that the unexpelled products of conception rapidly become necrotic and as such are a fertile field for the growth and multiplication of pathogenic bacteria. The radical plan was adopted three years ago and up to the present time results have been most gratifying.

The method is as follows: Upon admission, a cervical culture is immediately taken (using the technic described under Endometritis) and a twenty-four-hour report is requested. *Sulfadiazine* therapy is immediately instituted, giving an initial dose of 2 gm. followed by 1 gm. every four hours. The general condition of the patient is determined by thorough physical examination, complete blood count, blood sedimentation, and urine analysis in order to evaluate the





showed evidence of hemorrhage on post-mortem examination.

Potter concludes that no decrease in infant or fetal mortality can be expected to result from the routine administration of vitamin K to all women during labor.

Regardless of mortality statistics, the editor has noted a definite decrease in hemorrhagic manifestations in the newborn since routinely administering vitamin K to the infant immediately after delivery.

### Impetigo in Newborn

Since the offending organisms in impetigo contagiosa are considered to be predominantly staphylococcic or streptococcic, it was natural to try *penicillin* as soon as it became available.

Cohen and Pfaff<sup>61</sup> reported experiences in the U. S. Navy with the local application of penicillin in cases of severe impetigo which had not responded to the accepted therapeutic measures, *i. e.*, *ammoniated mercury* and *sulfonamide ointments*. These authors point out that the ointment was applied three times daily after removing the crust on the lesions, and observed "most gratifying results" in three to seven days, although the infection had withstood previous efforts at control from three weeks to three months. Templeton, Clifton, and Seeburg also reported the successful use of penicillin gauze or ointment in twelve cases of impetigo contagiosa.

Intramuscular injections of penicillin sodium had been effective to a gratifying degree in controlling previous outbreaks of impetigo contagiosa in the nursery. However, this form of injection therapy suffers from the disadvantage that the infected skin must be punctured several times daily with a hypodermic needle, thereby offering foci for new infections, and sterile abscesses are occasionally produced.

Gamble, Miller, and Tainter<sup>62</sup> report therapeutic success with oral administration of the new *benzyl ester* of *penicillin*. Fifteen consecutive cases of impetigo contagiosa occurring in the hospital nursery were treated with benzyl penicillin (Winthrop) after first being isolated. The material was dissolved in a strength of 25 mg. per cc. in sesame oil or in propylene glycol; the former is a bland oil commonly used as a solvent for lipiodol pharmaceuticals, and the latter is well known as a vehicle for vitamin D. The same dose was used for both preparations, *i. e.*, 0.25 cc. (10 drops) given every four hours before each regular feeding for a total of six doses in twenty-four hours.

One day of treatment (six doses) was sufficient to clear the lesions in two of the four infants given only the glycol solution, and a second day of treatment (twelve doses) cleared the other two cases. The sesame oil solution cured eight out of nine cases in only one day and in these there was a strikingly prompt cessation of the impetiginous process with the beginning of medication.

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## Rh BLOOD FACTOR

### Erythroblastosis

The term fetal erythroblastosis actually includes three distinct clinical entities: Fetal hydrops, icterus gravis, and congenital anemia of the newborn. Davidsohn<sup>63</sup> lists in chart form the sequence of interlocking pathologic changes possible.

Any one of them or any combination of them may be present or absent. Not one of them is absolutely pathognomonic for the disease except anti-Rh agglutinins, the presence of which in the mother suggests strongly fetal erythroblastosis in the baby. However, that, too, is not

an absolute rule. Davidsohn found several instances in which anti-Rh agglutinins were found in the mothers but the babies were born normal. The absence of anti-Rh agglutinins in the mother does not exclude the disease in the child, even if the Rh factor is responsible for the disease. It should also be kept in mind that a certain proportion (about 10 per cent) of cases of fetal erythroblastosis are not caused by isoimmunization by the Rh factor.

One may be able to prognosticate to some extent regarding the probable occurrence of erythroblastosis in future pregnancies, by examining all living children. If one of them is Rh—, the father is heterozygous Rh+ and his children have an even chance to be Rh+ or Rh—. The Rh— children will be free of erythroblastosis, at least as far as it is due to the Rh factor. Similar information is sometimes obtainable by examining the husband's parents. If one of them is Rh negative, the inference is justified that the husband is heterozygous Rh positive.

The relation between the Rh factor in the baby and erythroblastosis has been dramatically illustrated by several reports of erythroblastosis in Rh positive infants, while the Rh negative twins were free of disease. The best time to test for anti-Rh agglutinins in the blood of mothers of babies with erythroblastosis is not immediately after delivery but about ten days later. It is probable that, until birth, there is an interchange of antigenic substances and antibodies between mother and baby. The baby's antigenic substances may neutralize the specific antibodies in the blood of the mother. This explains the higher titer, after an interval of from ten to fourteen days since delivery, when possibility of neutralization has been eliminated.

Recent developments in isoimmunization by the Rh factor are discussed by Levine.<sup>64</sup>

(1) Erythroblastosis fetalis is the result of prolonged intrauterine reaction of maternal immune agglutinins and susceptible fetal blood; (2) at least 90 per cent of all mothers of erythroblastotic infants are Rh— and their husbands and the affected infants are Rh+; (3) in the smaller group of Rh+ mothers, finer differences within the Rh complex as well as several other blood factors other than Rh (such as the blood factor of Levine and Polayes, Hr, A, B, and perhaps others) may be responsible for isoimmunization of the mother; (4) Rh— immunized mothers can be safely transfused with Rh+ blood; and (5) the chances for survival of the affected Rh+ infants of Rh— mothers are better if they are transfused with Rh— blood.

However, the presence of anti-Rh agglutinins, which is direct proof of immunization, could be demonstrated only in about 50 per cent of the Rh— mothers even if tested soon after delivery. This difficulty has now been met with the demonstration independently by Race in England and Wiener that many Rh— mothers of erythroblastotic infants have anti Rh antibodies which specifically unite with and coat the surface of Rh+ blood, without inducing the visible effect of agglutination. In other words, the antibody is incomplete because only the first stage of the reaction, *i. e.*, specific union, occurs. The specifically coated Rh+ blood is now incapable of reacting with potent anti Rh agglutinins. Accordingly, Wiener called these "blocking" antibodies, while Race used the term "incomplete" antibodies. These significant findings were soon confirmed by several workers (Diamond, Fisk, and Morrow, and Levine). In the patient, however, the specific reaction goes to

completion so that the end result is hemolysis. In other words, clinically, one cannot differentiate erythroblastotic infants of mothers who have anti-Rh agglutinins from those whose mothers have the incomplete antibody. By the same token, both groups of mothers are subject to severe and even fatal hemolytic reactions if they are transfused with Rh+ blood.

controlled, nevertheless the outlook for Rh— women is now much better than previously. In the first place, one can prevent the deliberate isoimmunization of the Rh— female population by transfusions with R+ blood. Secondly, the blood of the pregnant Rh+ woman should be tested periodically to detect the earliest onset of isoimmunization. In general, failure to demonstrate antibodies throughout

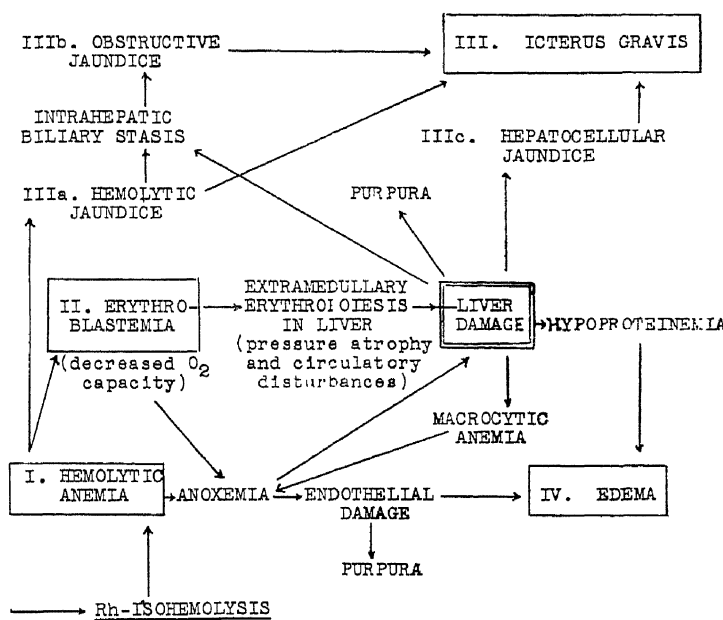


Fig. 10—Pathogenesis of fetal erythroblastosis. Principle: Rh positive husband of Rh negative woman transmits the Rh factor to the fetus. Rh antigenic substances pass from Rh positive fetus through placenta and produce in mother Rh antibodies. The latter pass from mother to fetus through placenta, act in the fetus as hemolytic agents and start the sequence of interlocking pathologic changes as presented in this chart. (Davidsohn, I.: J. A. M. A. 127: 633 (Mar. 17) 1945.)

The varieties of anti-Rh sera indicated a complex or mosaic structure of the Rh factor. Levine suggests that the obstetrician think only in terms of the one anti-Rh serum (diagnostic) which detects more than 90 per cent of all persons immunized either by transfusions, pregnancies, or a combination of both factors. For the study of the 8 per cent Rh+ mothers of erythroblastotic infants, the blood specimens should be referred to specialists in the field.

Although the silent process of isoimmunization by the fetus cannot be

the pregnancy make it possible to give a good prognosis. If antibodies are present and on the increase, the physician can make the diagnosis of erythroblastosis fetalis well in advance of the delivery. Premature induction of labor in selected cases in order to shorten the period of intrauterine hemolysis seems a logical procedure. No further pregnancies should be recommended until after the disappearance of all residual agglutinins or incomplete antibodies produced in the previous pregnancy. In addition to this, another interval of one

or more years should elapse before another pregnancy is attempted. In this manner, it is hoped to reduce the intensity of the isoimmunization in the following pregnancy.

Diamond and Denton,<sup>65</sup> of the Blood Grouping Laboratory in Boston, discuss the present concept of the best therapeutic procedures for the treatment of erythroblastosis fetalis.

Agglutinating antibodies (Rh agglutinins) may be demonstrated by the proper laboratory methods as emphasized repeatedly by Levine and by Wiener. In some cases the severity of erythroblastosis in the infant appears to be directly proportional to the titer of such agglutinins in the maternal blood; in other instances, however, there is little or no agglutinin demonstrable by the usual technic (incubation of a 2 per cent suspension of Rh positive cells with the unknown serum for thirty to sixty minutes) and these cases in general have the most severe manifestations of the disease. The explanation of this paradox was furnished by Wiener<sup>66</sup> and by Diamond and Abelson, who proved beyond doubt that inhibitor or blocking antibody is present in such instances and interferes with the usual laboratory technic for agglutination of Rh positive cells. The last mentioned writers also found that these inhibitor antibodies are most commonly present and tend to increase in concentration after repeated stimulation, thus being associated with progressively more severe erythroblastosis in successive infants. In the experience of the Blood Grouping Laboratory, there is a close correlation between this evidence of repeated stimulation (*i. e.*, blocking antibody) and the most serious forms of erythroblastosis, such as icterus gravis, fetal hydrops, and intrauterine death.

It has been demonstrated that with the proper tests for recognition of block-

ing antibodies in the blood (and these tests are very easily and simply applied by Diamond and Abelson<sup>67</sup>), the level of antibody does parallel the degree of sensitization and the severity of the disease in the infant.

Splenomegaly and hepatomegaly vary directly with the degree of red cell destruction and regeneration; pulmonary involvement, purpuric hemorrhages, edema, and other findings are manifestations of very severe and frequently terminal hemolysis associated with blocking of end capillaries with cellular debris. In view of this, the degree of anemia, rapidity of its onset and progress appear to provide the most reliable criterion for the institution of proper therapeutic measures rather than such indefinite signs as "toxicity."

Rh negative cells not only replace the destroyed erythrocytes of the erythroblastotic infant but, in addition, survive. On the contrary, transfused Rh positive cells are totally destroyed within three days. It seems, therefore, unsound to advocate the introduction of Rh positive cells, since the cellular debris resulting from their certain destruction may embarrass an already overburdened infant's system. The administration of *oxygen* is undoubtedly of value in the presence of anoxia; on the other hand, transfusion of viable erythrocytes seems the appropriate therapeutic approach to the problem of anemic anoxia. Intravenous glucose and saline solutions are not usually indicated as they tend to aggravate the edema and further embarrass the circulation.

Though it is certainly not desirable to impose too great prematurity on such a child, there is no doubt that two to four weeks of prematurity is a much slighter risk than the same period of time spent by the fetus in an environment where an increasing antibody ab-

sorption from the mother's circulation may produce more severe damage to the erythrocytes and secondarily to other important systems of the body. Statistics gained in the study of more than thirty families in which a previous child has succumbed to erythroblastosis support the opinion that earlier delivery of the next infant, especially in the face of an increasing antibody production on the part of the mother, results in a larger number of living children recovering from the disease.

Harville<sup>68</sup> advocates premature termination of pregnancy in patients in whom erythroblastosis fetalis is feared. The more drastic methods of inducing labor are probably best avoided, and if simple medical induction fails, it is felt that cesarean section merits consideration. Analgesia and general anesthesia are interdicted.

A neglected procedure which the author believes to be of the greatest value in the management of these prematurely delivered infants is the use of the umbilical vein for the initial blood transfusion. This is a technically simple procedure which involves minimum handling of the infant and obviates the traumatization incident to venipuncture, factors of vital importance in this critical initial period of premature management. Prothrombin, frequently deficient in erythroblastotic infants, is probably more promptly supplied in this way than by the vitamin K preparations also given routinely to these infants as well as to the mothers prior to delivery.

The simplicity of this method and the promptness of blood administration it assures commend it also for the initial transfusion of the full-term infant suspected of having erythroblastosis. It might well prove lifesaving in the occasional infant such as the one mentioned by Wiener, who he states would have

died had blood not been given within fifteen minutes of its birth.

The umbilical cord is clamped immediately after delivery to exclude the blood from the placental circulation, and 60 cc. of blood from a similar type Rh negative donor are given the infant through the umbilical vein. The author feels that it is the method of choice for the initial transfusion also of the full-term infant suspected of having this disease.

This, in the editor's opinion, is an excellent procedure but requires a great amount of teamwork, especially if the delivery occurs in the middle of the night.

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## STERILITY

### Rh Negative and Artificial Insemination

Further evidence to support the theory of maternal immunization to the Rh factor as a cause of erythroblastosis lies in the fact that an Rh negative woman who had given birth to infants with erythroblastosis was successfully impregnated by artificial insemination with Rh negative sperm and gave birth to a normal Rh negative infant. Potter and Wilson<sup>69</sup> cite the case of Mrs. A who at the age of thirty-one delivered a female child who was normal at birth and who is now alive and well and of blood group O Rh+. Three years later, she had a spontaneous abortion. The following year she again became pregnant and gave birth to female twins, both of whom exhibited clinical evidence of erythroblastosis. Both died, and the diagnosis was confirmed at postmortem examination. The blood of the patient was found to be A Rh—, the husband O Rh+. The twins were not tested.

In view of the existence of typical erythroblastosis in these offspring, it was

considered unwise for her to attempt further pregnancies except by insemination with semen from an Rh negative man. Approximately one year later, the patient was artificially inseminated on the fourteenth and sixteenth days of one menstrual cycle and on the thirteenth and fifteenth days of the following cycle. She did not conceive and two months later was inseminated on the eleventh and sixteenth days with sperm from another donor. Two hundred and sixty-eight days after the last insemination, she gave birth to a normal female infant whose blood is A Rh—. The infant is now two months of age and has had no symptoms of erythroblastosis.

The editor has found this to be a rather difficult treatment to recommend, especially to parents who have one normal child.

### Uterotubal Insufflation in Sterility

Strong proof of the therapeutic aspects of uterotubal insufflation in sterility is offered by Rubin.<sup>70</sup> Insufflation aids the sterile woman by:

1. **Establishing Patency of the Genital Tract**—If the external os appears punctate or pin-point but admits the cannula, this is proof that it is wide enough to admit semen into the external opening of the cervical canal. The cannula at the same time stretches it somewhat, rendering the canal more patent for a varying period of time. Should intercourse take place shortly after this procedure, the spermatozoa have a better opportunity to enter the uterine cavity.

2. **Removal of the Cervical Mucus Plug**—Rubin employs suction preliminary to the introduction of the cannula, thus clearing the cervical canal of the deeply lodged mucus plug.

3. **Effect on the Tubes**—Its manifold action consists in separating mild agglutinations of the folds of the tubal

mucosa, straightening out tortuous tubes, especially of the infantile type (this must be only temporary), dislodging a mucus inspissation from a narrow to a wider portion of the tube, and actually separating adhesions at the fimbriated end in cases requiring pressures of 150 to 200 mm. Hg or more. Ligated tubes were successfully reopened in this way.

4. **Possible Psychic Effect**—There are women who respond to insufflation through the psyche acting on the autonomic nervous system. This results in a relaxation of otherwise spastic tubes.

The therapeutic effect of repeated tests is emphasized by Rubin. As many as eighteen tests were performed on one of his cases. Twenty patients in his series, in whom a single test showed a pressure of 200 mm. Hg, nevertheless became gravid. In these cases either a small amount of gas was forced through strictured tubes, the amount being insufficient to produce a subphrenic pneumoperitoneum and shoulder pains, or uterotubal spasm actually resisted the passage of CO<sub>2</sub> at a pressure of 200 mm. Hg.

In Rubin's series, there were 2014 patients in the group of primary sterility. Of these, 358 (17.77 per cent) became gravid. There were 1186 patients with secondary sterility, of whom 232 (19.56 per cent) became pregnant. Altogether, 590 women were reported pregnant out of 3200 cases, making the total percentage 18.44. Insufflation was the only treatment employed in 386 of the 590 patients who became pregnant (65.42 per cent). Of the 590 patients, 247, or 41.86 per cent, had initial pressures above 100 mm. Hg, which may be taken as evidence of impaired patency. The therapeutic effect of insufflation is particularly noteworthy in the 94 cases in which pressures of 150 mm. Hg and over were required for the gas to pass through the tubes. Repeated insufflations

improved the status in many of these cases before pregnancy took place. In seven of the successful cases with high-grade strictures, lipiodol was also employed.

Rubin injected lipiodol in 159 patients and pregnancy followed insufflation and lipiodol in these 7 patients alone. If we omit 99 cases of tubal closure and the 7 cases in which the examination was unsatisfactory, the incidence of pregnancy in the remaining 53 cases is 13.21 per cent. This is less than half the percentage of success where insufflation alone was employed in the general group of patients having tubal strictures (31.13 per cent). Of the 590 cases of pregnancy, 11 were treated with small doses of radium for delayed and scanty periods and one received a larger dose for menometrorrhagia. Similarly, 29 patients had received x-ray and insufflation therapy before becoming gravid. Two hundred and twenty-eight patients, or 38.64 per cent, became gravid within two months after insufflation. Data of 517 women who became gravid after insufflation show that 419, or 81.04 per cent, had full-term babies.

Many of the patients who aborted belonged to the amenorrhea group. Ninety-four patients who became pregnant following insufflation subsequently encountered renewed difficulty in conceiving. Another insufflation was again succeeded by pregnancy.

Rubin reports in this series twenty-six cases of women who became pregnant within one month following this procedure. They were over thirty years of age, were sterile for a period of over five years, took no contraceptive precautions for at least one year, and resorted to no other treatment than insufflation.

The poor results with lipiodol are surprising and contrary to the editor's personal series. Repeated lipiodol insuffla-

tions in the office have given a higher percentage of pregnancies than tubal insufflation alone.

### Polycystic Ovaries in Sterility

The significance of bilateral polycystic ovaries in sterility is discussed by Stein<sup>71</sup> in a study of fifty-three patients who sought advice because of amenorrhea, sterility, or hirsutism. The diagnosis is made by a history of amenorrhea and/or sterility, and the discovery upon general physical examination of a masculine type of hirsutism, and, in many instances, hypoplasia of the breasts. Pelvic examination will often reveal the presence of a small uterus. While in some women the author can palpate definitely enlarged and globular ovaries, in the great majority he fails to find any abnormality and relies upon pneumoroentgenography.

Normally, the uterine shadow upon pneumoroentgenography is about four times the size of the ovarian shadow. In the case of polycystic ovaries, however, the ovaries may appear half as large or even the same size as that of the uterus. The ovaries may appear to be round, oval, elongated, or angular on the film, depending upon the position of the gonads in the pelvis at the time of x-ray.

The surgical technic of ovarian wedge resection for bilateral polycystic ovaries is as follows:

A Pfannenstiel incision is made and the enlarged ovaries are delivered into the operative field. Retractors may be removed and lap pads are not required in the peritoneal cavity. The ovaries are separately and successively held by means of a Scudder clamp covered with rubber tubing. A wedge is dissected from the ovary by sharp dissection, the size of which is determined by the amount of ovarian enlargement. The follicle cysts remaining in the ovary are punctured from within the ovarian incision, and tension is thus released. With No. 00 plain catgut, and a fine, full-curved, noncutting

needle, two rows of continuous sutures are used to close the wedge, the first row deep to the base of the wedge, locked at the end, and returned as a second superficial approximation suture. This leaves a single line scar. The clamp is removed, care being taken that compression of the ovarian vessels by the clamp lasts no more than twenty minutes (usually less than ten minutes is sufficient).

Fifty-three patients were treated surgically. Seventeen married patients and three of the single patients who subsequently married (a total of twenty) became pregnant after operation (64.5 per cent), resulting in twenty-six pregnancies and twenty-eight babies. This number was obtained as four women were pregnant twice, one three times, and there were two sets of twins.

Periodic checkup postoperatively revealed that there were no recurrences of bilateral polycystic ovaries. Three single women who had febrile and painful postoperative courses developed a unilateral ovarian cyst with adhesions (5 per cent).

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## MEDICINE

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### ACUTE INFECTIOUS DISEASES

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The impressive miracles of chemotherapy, under analysis, reveal problems that miracles will never solve. These problems go deeply, not only into the nature of infection, the nature of virulence, the nature of the infecting organism, the nature of the drug or other chemotherapeutic agent, but also into the multiple factors, genetic and environmental, that influence susceptibility and determine resistance. These problems will yield only to fundamental study that will elucidate the chemical and physical phenomena that constitute a complex and interacting three-way metabolism—of host, of organism, of drug, or other therapeutic agent.

The more scientifically motivated of the clinical trials of the sulfa drugs and the various antibiotics tend to attach less importance to the more easily measured factors (such as the number of apparent "recoveries," amount of dosage, time intervals in administration, and total length of treatment), and more importance to other imponderable factors, in-

cluding "complications," toxicity, the phenomenon of drug resistance, strain differences, the danger of producing a carrier state, the need of supplementing this or that miracle drug by "adjuvants" in the shape of other drugs or other nonspecific treatment. In these imponderable factors lie the true perspective for the study of chemotherapy.

The biological approach to bacteriology has contributed to a broader basic understanding of the processes of infection and "immunity." The focus of our present interest, as Sevag points out in his recent comprehensive study,<sup>67</sup> "must of necessity be the nature and the intensity of the chemical activity of micro-organisms, for these constitute their biologically indispensable characteristics and determine the nature and the fatality of the disease they cause." From the biological point of view, the disease, death, and immunity, in case of recovery, caused by the multiplication in a host, are "incidental events." The broader picture involves the biology of

the bacterium *per se*, the morphological and cultural characteristics, and the biochemical activities of bacteria in relation to the nature of infection. It involves, in particular, the enzyme activity of bacteria which motivates their growth and reproduction *in vitro* as well as *in vivo*, and the property which makes certain bacterial constituents antigenic. "Of these constituents, the protein is the most essential one." Understanding of the generally accepted facts that the production of antibody against an antigen is usually dependent on the protein molecule, and that the enzymic activity of a substance of biological origin is dependent on the presence of protein in the enzyme molecule, brings the whole study of infection into the realm of enzyme chemistry, and leads the way toward a more fundamentally scientific insight than now exists into the causation of infectious disease. Mudd regards the Sevag book as indicating for the first time the "fulness of the interaction possible between the fields of enzyme chemistry, immunochemistry, and the mechanism of infectious disease." "Much of the pathological symptomatology of bacterial and viral disease," Mudd points out, "may . . . ultimately come to be understood as special manifestations of enzyme action."

Of outstanding importance in chemotherapy is the manner in which the chemotherapeutic agent affects bacterial growth—by retarding it, as in the case of sulfanilamide; by inhibiting the parasite's use of the substances which protect it from the host, as in the antipneumococcal polysaccharidases; or by reacting with bacterial products which are injurious to the host, as do antitoxins. A beginning at least has been made in attempts to study correlations of the actions of agents upon the parasite *in vivo* and *in vitro*; upon the essential mech-

anism of synergism and antagonism; upon the finding of *in vitro* phenomena associated with drug resistance *in vivo*; and upon the type of change in the host associated with the success of chemotherapy or with normal recovery from or resistance to infection. The present empiric use of chemotherapy will become scientifically sound only when practitioners are continuously interested in and guided by the fundamental understanding of mechanisms that is being slowly developed in the laboratories.

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## BACTERIAL INFECTIONS

### Pneumococcic Infections

**Lobar Pneumonia**-- While the sulfonamides seem still to be preferred (in particular, *sulfadiazine*), especially at the beginning of treatment of lobar pneumonia, Blake<sup>1</sup> suggests that the physician should be prepared to shift to *penicillin* if toxic effects are significant or if response is delayed.

Penicillin has now been tried clinically in a number of cases of pneumococcal pneumonia. Kolmer,<sup>2</sup> analyzing reports of treatment in 102 cases, estimated a recovery rate of 87 per cent. These cases, reported from three research centers, included a large number having bacteremia. On the basis of these reports, it appears that intramuscular injections of 10,000 to 20,000 units, every three hours, day and night, are sufficient unless the infection is very severe or generalized. In such cases, intravenous administration is indicated, allowing 100,000 to 200,000 units per day, by the continuous drip method, followed by a course of intramuscular injections. Freedom from relapses and complications seems to be related to the length of treatment, which should be continued

for three or four days after the temperature has become normal.

**Other Pneumococcic Infections—**The most dramatic results from the use of the sulfonamides and penicillin have occurred in the treatment of pneumococcal meningitis. The death rate which, before the development of the sulfonamides, was from 90 to 95 per cent, has, by the use of these drugs, been reduced to about 45 per cent. Several recent reports<sup>3, 4</sup> showed improved recovery rates (approximately 70 per cent in several small series totaling 55 cases) with the use of penicillin, either alone or with the sulfonamides. These reports advocate the *intrathecal injection of penicillin*, combined with *intramuscular injection of penicillin* and *sulfonamides by mouth*. This treatment is judged to be superior to sulfonamides with serum, or sulfonamides or penicillin alone.

### Streptococcic Infections

The work of the last few years has revealed the degree to which the effectiveness of the sulfonamide drugs and penicillin is dependent upon the types and groups of streptococci dominantly involved in a given condition. The greater effectiveness of penicillin over the sulfonamides appears to be established<sup>1</sup> in the conditions due to the (Group) A Beta hemolytic streptococci, which are responsible for suppuration and necrosis with or without septicemia, in such conditions as: Severe cellulitis, mastoiditis, meningitis, pneumonia, empyema, pericarditis, endocarditis, puerperal sepsis, peritonitis, osteomyelitis, suppurative arthritis, and infected wounds. Group A Beta hemolytic streptococci are also responsible for less severe infections in which tissue invasion occurs without suppuration, necrosis, or bacteremia, such as erysipelas, lymphan-

giitis, ulcers of the skin, tonsilitis, and pharyngitis. *Penicillin* is indicated in all of these conditions, especially when they are due to sulfonamide-resistant streptococci or when the value of the sulfonamides is still debatable. A study<sup>5</sup> at Fort Bragg of forty-five cases of pharyngitis and tonsillitis due to hemolytic streptococcal infection resulted in the conclusions that whereas sulfadiazine suppressed but did not eliminate the streptococci, penicillin treatment, continued for six days, eliminated streptococci from the nasopharynx.

**Subacute Bacterial Endocarditis—**Streptococci of the viridans group are known to be only slightly, if at all, susceptible to *sulfonamide drugs*.<sup>1, 2</sup> A few years ago, the spontaneous recovery rate, in an analysis of 2956 cases of bacterial endocarditis associated with various types of viridans and nonhemolytic streptococci, was estimated as 1 per cent. In the same analysis, 409 cases treated with sulfonamides showed a recovery rate of 4 per cent. Six more recent reports indicate improvement in the recovery rate of cases treated with *penicillin*.<sup>3, 6</sup> Goernor, Geiger, and Blake<sup>6</sup> report a total dosage of from 3,900,000 units, daily, to 17,420,000 units, administered by continuous intravenous drip for periods of from 21 to 70 days. Loewe,<sup>7</sup> who combined heparin with penicillin, in fifty-four unselected, consecutive cases, some in so extreme a condition that any kind of therapy constituted a considerable hazard, reports approximately 75 per cent clinical cure, with thirty-seven of the forty that responded favorably now actively employed. Both groups consider intravenous injection the method of choice; both stress the need of stringent laboratory control of each case treated: Persistent bacteremia with a high or moderately high colony count of identical

organisms must be established and the sensitivity to penicillin of the organisms isolated in each case established before treatment is instituted. Both stress the need of massive dosage (the Yale group attributing the failure of an earlier trial of penicillin for subacute streptococcal endocarditis to inadequate dosage); Loewe<sup>7</sup> points out that under inadequate dosage the organisms may acquire a resistance to penicillin that makes further use of the drug impossible. Loewe, who used an average daily dose of 200,000 Oxford units, suggests that the best clinical results are achieved when the dosage of penicillin is sufficient to develop and maintain a blood serum level of five to ten times the sensitivity figure shown by the organism. His series of fifty-four patients revealed thirteen different organisms and three different species; no conclusions are given on attempts to correlate the type of streptococcus with its sensitivity to penicillin and the clinical response of the patient to penicillin. Goerner, Geiger, and Blake used penicillin alone; Loewe combined penicillin with heparin which, since experimental work in 1939, has been reported to have an erosive effect on the fibrin deposits which, with blood elements in endocardial vegetation, serve as an impenetrable barrier to effective chemotherapeusis by circulating agents.

**Prophylactic Use of the Sulfonamides in Streptococcal Infections—** Attempts to inhibit the development of infections by chemoprophylaxis were, in the first instance, directed toward the prevention of recurrence of streptococcal infections in patients who had had attacks of rheumatic fever. The mass trial of chemoprophylaxis of streptococcal infections by medical officers of the Army and Navy has been directed toward the prevention of rheumatic fever, scarlet

fever, and respiratory infections. The technics are not fully evaluated.

Morgan and Turner,<sup>8</sup> discussing the possible applicability of these technics to individuals, observe that it is not yet possible to determine how far the protection afforded the individual in mass prophylaxis is due to the drug that he himself takes and how far it is due to the fact that others in his environment are also receiving the drug. It is also pointed out that the military personnel with which the study deals is a highly selected group. Toxic manifestations might be a greater hazard in a less highly selected group. Morgan and Turner suggest that the physician, in determining the desirability of prophylaxis for a given individual, must consider whether the patient is a member of a group subjected to an epidemic to which mass prophylaxis is not available. The other consideration is whether the individual is especially liable to frequent and severe disabling respiratory infections.

As a result of 1 gm. daily of *sulfadiazine* taken in the evening, in a trial of prophylaxis among military personnel, only one in ten developed scarlet fever, and one in six developed infections of the upper respiratory tract of sufficient severity to require hospitalization.<sup>8</sup> Morgan and Turner look hopefully toward the practical use of sulfadiazine in preventing repeated attacks of rheumatic fever. While the most desirable dosage has not yet been established, they suggest extensive trial of 1 gm. daily of sulfadiazine with unremitting watchfulness for the signs of drug sensitivity during the first four weeks. On the basis of experiments with large numbers of military personnel, sensitivity may be expected in from 4 to 5 per 1000 individuals. If no reactions occur, uninterrupted year round chemopro-

phylaxis is the best safeguard against acquired sensitivity. Severe reactions pointing to withdrawal of the drug were found to occur in 1 out of 100,000.

### Staphylococcic Infections

Blake<sup>1</sup> states that *penicillin* is "unequivocally the drug of choice" for treatment of furunculosis, carbuncles, osteomyelitis, mastoiditis, with or without intracranial complications, meningitis, sinus, thrombosis, pneumonia, lung abscess, empyema, pyelonephritis, and wound infections with or without staphylococcemia.

**Staphylococcic Septicemia**—The mortality in cases of staphylococcic septicemia before the availability of the sulfonamides was generally agreed to be between 85 and 90 per cent.<sup>2</sup> Of the sulfonamide compounds, *sulfathiazole* has proved the most valuable, but in meningeal involvement, since *sulfathiazole* does not reach the cerebrospinal fluid from the blood stream, *sulfapyridine* is more valuable. Sulfonamide therapy has reduced the mortality rate from septicemia to about 70 per cent.<sup>2</sup>

Reports within the past year, covering sixty-five cases of penicillin therapy (in five series) showed fifty-one recoveries (a mortality rate of 16.6 per cent). Failures may be due to the fact, recently demonstrated, that some strains of staphylococcus contain a substance antagonistic to penicillin, which may be similar to the enzyme penicillinase found in colon bacilli.<sup>1</sup> In these cases, and in other very severe infections, *oral sulfathiazole* therapy is recommended in addition to *penicillin*.

**Other Staphylococcic Infections**—Trial has been made of *penicillin* in fifteen cases of staphylococcic pneumonia (either metastatic, following septicemia; or primary) with a reported recovery

rate of 80 per cent. Harford *et al.*<sup>3</sup> treated with penicillin eleven cases of metastatic pneumonia complicating septicemia, with only one death.

While acute osteomyelitis, which is often secondary to bacteremia, has been shown previously to respond to needle aspiration and *sulfathiazole*, the results in chronic osteomyelitis have been less satisfactory.<sup>3</sup>

Three recent cases of penicillin therapy for acute staphylococcic endocarditis (which, in a review of ten cases a few years ago, Keefer *et al.* reported as uniformly fatal) are now reported from the Washington University School of Medicine: Two of them after *penicillin therapy* are "apparently well" after two months and four months respectively.<sup>3</sup>

### Meningococcic Infections

From a study of 116 cases in a United States Naval Hospital, Whitaker<sup>9</sup> stresses the importance of early diagnosis in relation to the value of chemotherapy. He defines three phases of meningococcal infection: (1) The nasopharyngeal; (2) the septicemic or invasive, and (3) the meningeal. He believes that failure to recognize the signs and symptoms of the second (septicemic or invasive) phase has often led to delay in treatment and consequent high mortality.

The value of typing meningococci obtained from the nasopharynx in the midst of an epidemic of meningococcic infections is stressed by Branhan of the United States Public Health Service.<sup>10</sup> This worker states that since epidemics are normally due to Group I strains, chronic carriers of Group II strains are less menacing than temporary carriers of Group I strains. She recommends as quick and easy the application of

both the Neufeld "quellung" reaction and of the Noble rapid agglutination technic.

In therapy, the testimony seems to be that the clinical response to *penicillin* is slower than the response to the *sulfonamides*. Recent reports of sulfonamide therapy confirm the favorable results of earlier years. One recent series of ninety-one patients<sup>9</sup> treated with *sulfadiazine* (fifty-one of whom also received antitoxin, in addition) showed a mortality rate of 1.72 per cent, with no evidence of benefit received from the antitoxin. Various trials with penicillin, however, show a mortality rate approximately the same as the mortality rate with various sulfonamides.

The recently reported program of mass sulfadiazine prophylaxis confirms the findings of earlier years as to its value: In a recent study,<sup>63</sup> an epidemic of cerebrospinal meningitis was completely stopped among 18,000 men who received three oral doses of sulfadiazine: 2 gm. at 1 P. M., 2 gm. at 7 P. M., and 1 gm. at 7 A. M. Evidence of hypersensitivity and toxic manifestations in this series was minimal.

### Gonococcic Infections

As a result of the application of the sulfonamides and penicillin, Mahoney and Van Slyke<sup>11</sup> suggest that the incidence of gonorrhea may be drawing toward a point where it will "not be an important source of ill health to the human race," or a major public health problem. The usual wartime upward swing in the incidence of the disease has not thus far taken place. Mahoney and Van Slyke point out that before sufficient time had elapsed to make possible a real evaluation of *sulfonamide therapy*, *penicillin* was found to possess "an almost miraculous efficacy in checking gonococcic infections."

The sulfonamides are still in use, however, in both this country and in England. One military officer, for instance, recently reports<sup>12</sup> 79 per cent of cures with massive doses of sulfadiazine. The twelve cases in this series that were not benefited by sulfadiazine were cured by penicillin.

The phenomenon of resistance of strains of gonococci to the sulfonamides has fundamental bearing upon the whole question of the mechanism of chemotherapy. It has been known since the beginning of sulfonamide therapy in gonococcic infections in 1936 that a certain percentage of patients, about 15 per cent with the most extensively used compound, *sulfathiazole*, have failed to respond to this treatment.<sup>11</sup> This phenomenon was explained in general terms of either natural or acquired resistance to the sulfonamide compounds on the part of certain strains of gonococci. Specific data are lacking on the metabolic factors in host, organism, and drug that influence drug resistance. The point that is entirely clear is that patients infected by the same source have exhibited varying responses to the sulfonamides.<sup>11</sup> Cases are recorded that have been resistant to sulfonamide treatment but have yielded (on the basis of bacteriological and clinical findings suggesting cure) to penicillin.

For the effectiveness of penicillin therapy in gonorrhea, there is various recent testimony: In one series<sup>13</sup> of 100 cases, 95 cases (receiving 5 doses - - 100,000 units - - at 3-hour intervals) showed negative smears four hours after the last injection. Cultures for all cases were negative in twenty-four hours. Blake<sup>1</sup> believes that consistent experience now indicates the use of penicillin in all cases of gonococcic infection complicated by arthritis, ophthalmia, endocarditis, pericarditis, peritonitis, epididymitis, and

prostatitis. "Dramatic response" has been noted in reports on small numbers.

A group of public health officers in federal, county, and city venereal disease services present results which, in their judgment,

"Do not justify the prevailing optimism held by the public and many of the medical profession as to the efficacy of penicillin as an easy, infallible cure of gonorrhea."<sup>14</sup>

They stress the fact that the widely advertised 95 to 100 per cent cures are not borne out by their own work which, in a series of 485 gonorrheal patients, treated with an initial course of 200,000 units of penicillin, showed 68, or 14 per cent, not cured. They admit that penicillin will cure most cases of gonorrhea, but stress the point (included in various other reports of clinical trials) that cure is not necessarily accomplished by the first course of the drug or by penicillin alone. They counsel a better understanding of the limits as well as of the effectiveness of penicillin and suggest taking into account the possibility of producing a carrier state.

### Bacillary Infections

**Tuberculosis** — Attention continues to be focused on the hope of a specific chemotherapeutic agent against tuberculosis with continuing investigation of the sulfonamides and sulfones and rising interest in antibiotic substances.

Since Rich and Follis, in 1938, first reported sulfanilamide as having an inhibiting effect on experimental tuberculosis in the guinea pig, other workers have demonstrated the same effect on the experimental disease in the same animal, using a variety of *sulfonamide and sulfone compounds*.<sup>46</sup> These results in the experimental animal are considered a landmark, but certainly not the consummation, in the search for an effective specific chemotherapeutic agent for tuberculosis in man. Because of the

demonstrated effects of these compounds in the guinea pig, Corper and Cohn<sup>47</sup> investigated the specific mechanism of action of one of the most discussed sulfones, *diasone*, in this animal. On the basis of their experiments and reports of clinical trials, they account for the inhibitory effect of diasone on the tuberculous process in the guinea pig on the basis of the drug's cyanotic effect on the pig's internal organs, and the production of anoxemia in the animal, rather than by specific bacteriolytic or bacteriostatic action. Since they found that patients treated with diasone for months did not display an effect of anoxemia, they regard it as doubtful whether a therapeutic effect has been attained clinically in tuberculosis in man with the sulfonamide or sulfone drugs thus far. They add, "because of the greater sensitivity of the human being to anoxic and anoxemic effects, and the fact that such a mechanism appears to explain the favorable results noted on the tuberculosis in the guinea pig," human experimentation with these drugs at present would not seem warranted. In view of these findings there is interest in an abstract, in a recent issue of the *American Review of Tuberculosis*, covering the report of two French physicians who, after administering diasone (1 gm. daily, in 3 doses, for 120 days) to thirty cases of pulmonary tuberculosis, reported cyanosis in 90 per cent, besides other signs of toxicity; these workers concluded that diasone had no beneficial effect.

The general preoccupation with antibiotic substances is reflected in work in tuberculosis by the revival of interest<sup>48, 49</sup> in the tuberculocidal effect of these substances, neglected since Vaudremar in 1912-1913, demonstrated that filtrates of *Aspergillus fumigatus* would render human tubercle bacilli inactive

for guinea pigs. The products of numerous other strains of *Aspergillus*, as well as strains of *Streptothrix* and *Penicillium*, are now being studied for their lytic and inhibitory effects upon various strains of tubercle bacilli *in vitro*. Several centers in Britain and this country have also begun to study the effects of several of these substances ("helvolic acid," aspergillin and, most recently, streptomycin) on human tubercle bacilli in the guinea pig. Smith, of the National Institute of Health, which has been exploring the tuberculocidal properties of antibiotic substances for several years, notes that *streptomycin*, combined with *promin*, yields better results in guinea pigs than either, when used alone; the superior effects of the combination are attributed to synergism.<sup>50</sup>

The possibility of *vaccination* in tuberculosis is still being explored in animals. No other long-term, large-scale trial of vaccination in humans has been published since last year's summary of the results of a trial initiated in Jamaica in 1932 by the Government of Jamaica and the Rockefeller Foundation, of vaccination with a heat-killed tubercle bacillus on the basis of which the authors suggest that heat-killed vaccine would be valuable as protection for persons subjected to unusual risk of tuberculous infection, as, for instance, medical students, pupil nurses, etc.

**Leprosy**—Investigations of the possibility of chemotherapy for leprosy, pursued hopefully with a variety of substances during the last decade, are now directed, as in so many other infections, toward the sulfones. Faget, medical director of the National Leprosarium, and Pogge,<sup>51</sup> on the basis of a fairly long trial of promin with 137 leper volunteers, concluded that while promin "cannot be proved . . . to be a specific for leprosy . . . or to possess

any chemotherapeutic properties against leprosy" (since the causative organism, in spite of continuing efforts, cannot yet be cultivated on artificial media, nor can the human disease be reproduced in laboratory animals), its action in this series suggests a chemotherapeutic action since it has "at least an inhibitory effect on the progress of the disease and even causes retrogression in some lesions." They add that "the longer the duration of treatment, the greater the percentage of improvement."

**Pertussis**—What remains of the pertussis problem, according to Sauer<sup>53a</sup> is "*to prevent pertussis during the early part of the first year of life*" in which, although the incidence of the disease is lower than in older age groups, the mortality rate is considerably higher. Seventy-five per cent of the deaths due to whooping cough occur in infants under six months, and 6 per cent of the deaths of infants under one year, in New York State, for instance, are caused by whooping cough. Attack on this question is being made in biological studies attempting to learn more about the causes for the presence or absence of immunity in the first year of life, the ability of infants to develop active immunity, the operation of immunity in infants, the nature of antibodies that cross the placenta. Practical studies along these lines are reported in the current year: Kendrick and Eldering,<sup>54</sup> noting that newborn babies, although they have a high degree of resistance to measles, scarlet fever, and diphtheria, appear to be susceptible to whooping cough from the day of birth, report the results of a study of ninety-nine pregnant women, fifty-seven of whom were immunized with their vaccine, while forty-two were not. The findings (based on the ratio of opsonin titer of the vaccinated mothers to that of the unvaccinated controls during preg-



nancy and after the birth of the children, and of comparisons of the opsonin titer of the newborn infants in the two groups, and of comparisons of the opsonin titer of infants with that of their mothers in both groups) suggest that the higher the level in the mother, the more nearly does the titer of her baby approach her own, and that vaccination of the mother during pregnancy increases the titer of both mother and child.

On the results of immunization for very young infants: Sako *et al.*,<sup>53</sup> in a report on vaccination of 3783 infants, all under three months, most of them under two months, note that in the vaccinated group of 1834 infants, there were no deaths in the 159 subsequently exposed to infection within their own families, or the 153 exposed to contagion in clinics, neighborhood, etc.; while in the unvaccinated group of 1965, there were 13 deaths in the 149 exposed to infection in the family and 2 deaths in the 165 exposed in clinics and neighborhood.

Since there is no dependable test as yet for immunity—which can only be measured by the attack rate in the limited number proved to be subsequently exposed—both reports are still in the nature of experimental suggestions.

As to the status of prophylactic vaccination in children over a year: on the basis of a number of wide-scale public health trials (during the last six years) reporting a reduction in attack rate as the result of prophylactic vaccination, the Council on Pharmacy and Chemistry of the American Medical Association which in 1928 had deleted from *New and Nonofficial Remedies* the pertussis vaccines which this volume had listed from 1914 to 1928 (on the ground that they had not proved their worth in that period) authorized Felton and Willard to report on the status of prophylaxis of

H. pertussis infections. No further statement has followed the Council's 1944 adoption of the report for publication and the Council's announcement that it would "now consider for *New and Nonofficial Remedies*, H. pertussis vaccines prepared according to the method of Sauer, or of Kendrick and Eldering, or of Harrison and Bell." The vaccines have not been included in the 1945 issue. On the basis, however, of a number of published reports, including that of 1939, by the Committee on Administrative Practice of the American Public Health Association (analyzing the results of the 44-month controlled studies in Michigan) and the 1943 report of the Committee on Therapeutic Procedures for Acute Infectious Diseases of the American Academy of Pediatrics, the three vaccines named above are being tried and compared and evaluated on an increasing scale<sup>52, 53</sup> in various public health departments and clinics.

In therapy, interest attaches to wider trials with infants in clinics of a combination of *sulfadiazine* and *immune serum*. Reports last year covering a small series noted a rapid and permanent disappearance of the whooping cough bacilli from the respiratory tract. Although it has been known for some years that the sulfonamides are of value in the complications of whooping cough, studies aiming to investigate the value of these compounds against the organism itself are more recent.

**Bacillary Dysentery**—The disability caused by various enteric infections in the armed forces has again focused professional and public interest on bacillary dysentery. Felsen attributes the fiftyfold increase reported in bacillary dysentery between 1933 and 1944 in part to better differentiation of bacillary dysentery from various undetermined "infectious diarrheas" and in part also

to an actual increase in incidence. In spite of the enthusiastic claims made for the sulfonamides, which some physicians consider have revolutionized the treatment of bacillary dysentery, the current literature reveals considerable difference of opinion concerning the value of the sulfonamides, concerning the superiority of one compound over another, concerning their effect on the carrier state.

Keefer,<sup>60</sup> in summing up progress in the conquest of various bacteria by new chemotherapeutic agents, notes with regard to the use of sulfonamides:

"The fatality rate in bacillary dysentery at present is less than one half of one per cent, and the average number of hospital days for its victims has been between fourteen and sixteen days. The acute symptoms have frequently disappeared within seventy-two to ninety-six hours—a phenomenal change."

Felsen<sup>59</sup> believes that

"Final evaluation of sulfonamide therapy in acute bacillary dysentery awaits more accurate criteria than those commonly presented in the literature."

Among workers experimenting with the *sulfonamides in vitro* and in clinical trials, there are marked differences of opinion as to the relative value of sulfanilamide, sulfathiazole, sulfaguanidine, sulfadiazine, sulfapyrazine, sulfasuxudine, against *Shigella* organisms of various types. Hardy,<sup>57, 58</sup> on the basis of a long-term study of several epidemics of bacillary dysentery in various parts of the United States, reports a comparison of 10 sulfonamides used with 1423 cases of bacillary dysentery (in which Flexner, Sonne, and Schmitz varieties were isolated):

"Considering toxicity, availability and relative efficacy, it is concluded that *sulfadiazine* is the drug to be recommended for *Shigella* infections. . . ."

Appreciation of the extent of toxic reactions is still perhaps inadequate: One British worker, for instance, re-

ports reactions, some of them severe, in every one of forty-four women treated with *sulfaguanidine* for Flexner dysentery.

The questions of dosage and drug-resistant strains are also unanswered. Hardy<sup>58</sup> observes:

"Organisms isolated after seven or more days of treatment, if tested *in vitro*, were commonly found to be highly resistant to sulfonamides. The problem of treating Sonne infections appears to be related in part to the ready development of sulfonamide-resistance by these organisms. . . ."

Felsen, however, relates some of the failures to dosage rather than drug resistance on the part of strains.

"Failures, relapses and development of carrier states following sulfonamide therapy appear to be due generally to inadequate dosage (late starting or early discontinuing) or the presence of sulfonamide-resistant strains. . . ."

"Although some investigators deny a direct clinical relationship between sulfonamide dosage and clinical effectiveness, the general opinion at present appears to be as follows: the initial dose should be 0.16 gm. per kilo of body weight during the first twenty-four hours, in divided doses for four hours. Thereafter half the initial dose, until the symptoms recede and for a minimum of several days after that."

### Rickettsial Infections

**The Typhus Group**—Work in various laboratories in this country and abroad on epidemic and endemic typhus—on the possibility of chemotherapy; on the evaluation of various vaccines; on methods and procedures for prolonging the duration of immunity conferred by present vaccines—has, in the last two years, given way temporarily to the urgent need of more knowledge of Tsutsugamushi disease (scrub typhus, mite-borne typhus) prevalent in the Pacific war areas, especially endemic in Japan, and considered "a health hazard of paramount importance to American troops."<sup>61</sup>

Several laboratories in this country, military and naval groups here and abroad, have therefore addressed themselves to methods of cultivating the organism for the production of effective vaccines (not yet achieved) and to searching for a specific chemotherapeutic agent. While progress has been made in observations on the clinical course and pathology of this disease, on its epidemiology, on the relation of strains, etc., in the studies of Blake, Maxcy, Sadusk, Kohls, and Bell,<sup>62</sup> organized under the United States Typhus Commission, neither a vaccine nor a chemical specific for the disease has been developed.

Serotherapy, the therapeutic hope of experimental work in several laboratories in recent years, has been clinically tried in a few cases of Rocky Mountain spotted fever and of epidemic typhus with encouraging reports in both diseases if the hyperimmune rabbit serum tried is used early in these conditions. It is now being tried in experimental infections of scrub typhus.

### Virus Infections

The hope dies hard of dealing with virus infections by chemotherapy. It remains true, however, that the exceptional viruses that have responded in any degree to the *sulfonamides*—for instance, the viruses of trachoma, inclusion conjunctivitis, lymphogranuloma inguinale—are the large viruses, those nearest to bacteria. Current trials of *penicillin* against various viral agents of human disease seem to repeat the general failure of the sulfonamides. Some recent experimentation suggests an apparent but not a dramatic response to penicillin on the part of experimental psittacosis, again one of the larger viruses.

Stanley observes<sup>34</sup> that thus far only two basic procedures have contributed

to the control of virus diseases, *i. e.*, *vaccination with active virus* (the active virus either modified by passage through an unnatural host; or unmodified but injected by an unnatural route; or used, unmodified, with immune serum) resulting in an immunity depending upon the production of the virus in the host; and *vaccination with inactivated virus*, a development that is more or less recent, because of the persistent belief that inactive virus is inadequate to produce immunity. The present trend is to attribute past failures in the use of vaccination with inactive virus to inadequate dosage, or to faulty inactivation, too little exposure of the virus to irradiation or formaldehyde leaving it active, and too great exposure decreasing the antigenicity and immunizing potency of the resulting vaccine.

**Immunity in Virus Diseases**—Understanding of immunity to virus disease has, as Francis recently pointed out, required constant modification as information has developed. In virus, as in bacterial immunity, a hopeful trend is to lay less stress on specific conclusions as to the definite length of immunity possible in the various virus diseases, and to stress more the influence upon immunity of such factors as the mode of infection, the character of the disease, strain differences, and the availability of antibodies as at the portal of entry. On many levels, scattered studies, most of them still far from the possibility of practical application, concern factors that may influence the nature of virus immunity as, for instance, the observed interference of one virus with infection by another (interference phenomenon); and the surprising observation that malnutrition has appeared, in certain experimental poliomyelitis studies, to increase rather than decrease resistance.

On the moot question of what determines the duration of virus immunity, Francis, somewhat challenging the proposal that the duration of immunity is determined by the continued presence or absence of virus in the recovered animal, leans rather to the idea that the availability of antibodies is the deciding influence. Francis thinks it is important to consider the protective action of antibodies in terms of whether the agent attacks cells which are comparatively extravascular or cells intimately associated with the circulating blood; cells readily reached by outside agents, or accessible chiefly *via* the vascular system. "If the virus effects its entry into an environment where antibodies are readily available, it is prevented from establishing itself, either locally or at a distant point, and immunity to infection obtains; the protection of specific cells results in general immunity. If antibodies are not effective at the portal of entry but are present in the circulating blood, infection can take place with or without characteristic signs of the disease. When the injury at the portal of entry constitutes the essential manifestation of virus action, both infection and clinical disease occur though the latter may be limited in extent; when the establishment of virus at the primary site constitutes merely the starting point for its dissemination to distant tissues where the conspicuous damage takes place, infection occurs but the typical disease is prevented."

#### **Primary Atypical Pneumonia—**

Careful observers of many cases of primary atypical pneumonia dissent from the frequently expressed theory that, since the mortality from this disease remains low, it is not a stern challenge to medical practice. In spite of the technically low mortality rate, this syndrome ranks high in the list of disabling

diseases and its complications and sequelae are not yet thoroughly understood. Dingle,<sup>36</sup> director of the Army's Commission on Acute Respiratory Diseases, in summarizing the status of research on the etiology of this syndrome, observes that it "may be produced in its essential characteristics by a variety of agents, including bacteria, fungi, rickettsia, and viruses." Supporting the suspicion that a virus is the etiologic agent was the finding of the Commission (in its third attempt to transmit the disease to human volunteers, an attempt successful in infecting a proportion of those inoculated), that "primary atypical pneumonia is at least initiated, if not caused by a filter-passing agent, presumably a virus."

Considering the traditional stress on the imperative need of x-ray diagnosis in this condition, there is interest now in the observation of various observers that many cases of primary atypical pneumonia present an x-ray appearance not easily distinguishable from pneumococcal or other bacterial pneumonias, and that the clinical symptoms, the clinical course, and the laboratory findings must be taken into account with the interpretation of the x-ray. Golden, analyzing the pathologic anatomy in twenty-one of ninety cases of "atypical pneumonia, etiology undetermined," collected by the Central Pathologic Laboratory of the United States Army, stresses the need of routine x-ray and correct interpretation for the recognition of the acute interstitial pneumonitis of primary atypical pneumonia. Various workers stress the need of a chest roentgenogram, not only at the discharge of a patient but also at a later period. This counsel suggests recognition of the hazards of the characteristic sequelae of primary atypical pneumonia.

Treatment remains symptomatic; neither sulfonamides nor penicillin influences the course of this syndrome.

**Influenza**—While routine use of influenza vaccination for individuals has certainly not yet been achieved, there is accumulated evidence that mass vaccination is effective: The two large scale trials made in 1943-44 by the Army's Commission on Influenza and the International Health Division of the Rockefeller Foundation demonstrated a reduction in attack rate of 25 and 35 per cent respectively, in comparison with unvaccinated controls. But the vaccination is effective only for short periods of time, ranging according to various estimates from a month to eight weeks. Numerous articles<sup>34, 35, 38</sup> in the 1945 literature evaluate the data now available on these large-scale trials. The June 1945 issue of the *American Journal of Hygiene* reviews the findings of the several laboratories that cooperated. Francis, in the opening article, expresses the belief that all the data available through the Army Commission's studies

"Show for the first time clearly that subcutaneous vaccination of a human population with inactivated influenza virus vaccine exerts a pronounced effect upon the susceptibility to influenza A, during an epidemic of high incidence. . . ."<sup>38</sup>

Investigative work continues to explore the relative merits of various strains for use in vaccines, the amount of virus that can be used without toxic effect, the methods and materials that may prolong the present limited period of immunity, the possibility of strengthening and lengthening immunity by multiple rather than single doses, or by the use of adjuvants of various kinds with the vaccine virus.<sup>39</sup>

**Poliomyelitis**—There is continued emphasis on the alimentary tract as at least one important route of infection.

Pertinent to this thesis is the accumulated evidence supporting the long-standing suspicion of epidemiologists that flies may act as vectors for the virus. The New Haven workers, Paul, Ward, *et al.*, who have long been interested in the finding of the poliomyelitis virus in sewage and feces, conclude that their experiments in feeding to chimpanzees food exposed to flies in the homes of patients in recent poliomyelitis epidemics (in North Carolina, New York, and New Haven) "seem to remove any doubt that food exposed to flies . . . in an epidemic area may acquire a quantity of poliomyelitis virus sufficient to produce in chimpanzees by oral administration a nonparalytic infection or asymptomatic carrier state. . . ."<sup>40</sup>

While, in therapy, the controversy on the Kenny method still exists, there is perhaps a tendency toward greater objectivity in comparing the results of all available methods including hers. Green, director of clinics for the Harvard Infantile Paralysis Commission, after comparing a series of twenty-three cases treated in 1941 by the method evolved by the Commission with a series of twenty-one cases treated in 1943 by the Kenny method, arrived at no striking comparisons. In a summary evaluation of improvements a year after onset, the figures given suggest a slightly better result with the Commission's method, but Green adds that the "differences are not interpreted as necessarily significant" and are "within the limits of variation which will be found in comparing two groups of patients treated by the same method." His general conclusion is that while the Kenny method is not revolutionary in its results, "from my experience with this method, certain modifications in treatment have arisen which seem to be helpful in certain phases of the disease."<sup>41</sup> This is less

positive than Krusen's observation (of several years ago) that the enthusiasm for the Kenny procedures "seems to be, to a large degree, warranted." In any case, an increasing number of students of poliomyelitis, without attaching to muscle spasm the etiological importance which Sister Kenny ascribes to it, tend to feel that her treatment has served a valuable purpose in stimulating the investigation of the mechanism of muscle spasm and the rationale of *physical therapy* in the treatment of poliomyelitis.

There is no recent conclusive data on the use of *neostigmine* for the relief of muscle spasm or on nerve crushing; both procedures are known to be under trial in several clinics.

**Measles**—Since the morbidity rate of measles has not shown the decline of other infectious children's diseases, it is natural that investigative work should be directed toward the possibility of conferring *passive immunity*, through the use of *convalescent serum*, *McKhann's placental extract* and, to a more limited degree, normal *adult serum*. The importance of *gamma globulin*, as the most recent addition to this list, lies (1) in the higher concentration of antibodies that can be achieved in fractionated serum; and (2) in its greater availability (increased by the release in July, 1944, of surplus immune serum globulin for measles, designed for the armed forces). Large-scale public health experiment has now supplemented the first preliminary clinical studies demonstrating the value of gamma globulin in the modification or prevention of measles.<sup>42</sup> No final conclusions are drawn yet on its relative efficacy, as compared with convalescent serum, normal adult serum, or McKhann's placental extract. Gamma globulin as now prepared *must not be used intrave-*

*nously*. Stokes and his associates, and Janeway, agree substantially as to dosage for children (0.1 to 0.075 cc. per pound of body weight, by intramuscular injection, given as early after exposure as possible, for protection; and, for modification, one fourth the protective dose, on the fourth or fifth day after exposure).

**Rubella** (German measles) — The current year notes no addition of data to that of the last three years, regarding the congenital malformations, especially of the eye and heart, reported to occur in children born of mothers who have had German measles during pregnancy. There is reason, however, for careful clinical observation and record of such sequelae to this condition, traditionally regarded as one of the most innocuous of the virus infections. The possibility that other viruses may also constitute a hazard to the fetus in maternal virus infections during pregnancy has been related to the special susceptibility of embryonic tissues to viruses, illustrated by the wide current use of the chick embryo as a culture medium for many of them.

**Yellow Fever**—There are no significant additions to the work on yellow fever vaccination since the Army's Special Commission, investigating postvaccinal (yellow fever) jaundice, following 28,585 cases (with 62 deaths), after the use of serum-based vaccines in the United States Army, recommended that only *serum-free vaccines* be employed. An aqueous-based vaccine is now used.

**Infectious Hepatitis**—Although it is generally assumed that both infectious hepatitis and postvaccinal hepatitis are caused by a virus, and although both infections have been experimentally transmitted to human volunteers by the injection of substances taken from patients, it has not yet been demonstrated conclu-

sively that a virus is the cause of either or both conditions, or that the viruses causing the two conditions are identical. There are now, as there have been for the last two years, several schools of thought: Those that believe that both conditions are caused by a virus, but that the viruses are distinct; and those that believe infectious hepatitis and post-vaccinal jaundice are both due to the same or, as Findlay *et al.* put it, on the basis of complement fixation, in a series of clinical, epidemiological, pathological, and immunological studies, "very closely allied agents." In a different direction, the International Health Division of the Rockefeller Foundation points out that neither the epidemic nor the serum type of jaundice has been transmitted to experimental animals and, while there are many points of similarity in their clinical features, there is as yet no experimental evidence that the two are identical, and that the possibility of a toxic factor "operating alone or together with a viral agent has not been excluded." There seems to be general agreement that the incubation period differs in the two diseases: from twenty-five to thirty days for infectious hepatitis, as against two to four months for postvaccinal jaundice.<sup>43</sup> One new approach to infectious hepatitis is noted in the prophylactic use of *gamma globulin* during the incubation period: Havens and Paul note "a sharp difference in the rate at which jaundice occurred in the children inoculated with gamma globulin, as compared with a large group of uninoculated controls in the same institution," in an institutional outbreak of infectious hepatitis among children—among whom it is most common in this country, during ordinary times.<sup>44</sup> These workers, however, reflect the prevalent confusion, in observing that "there may be a number of different types of infec-

tious hepatitis . . . as well as a number of varieties of the related condition known as homologous serum jaundice," a possibility which, they consider, prevents any assumption that the prophylactic injection of gamma globulin would have the same results in all cases and all types of jaundice.

The importance of the etiology of postvaccinal hepatitis goes far beyond its rôle as a complication of yellow fever. The increasing use of fractionated products of serum and plasma—for blood transfusion, prophylaxis, and serotherapy—makes it important to consider, with reference to many other conditions besides yellow fever, how great is the hazard that jaundice may result from the use of serum and serum products. There have been scattered reports of jaundice following the use of pooled serum for measles, and of convalescent serum for mumps, of reconstituted dried human serum and of pooled human plasma for blood transfusion. Janeway, in reporting recent trials of gamma globulin for measles, observes that while he has not yet found any cases of jaundice, careful observations and records should be kept to establish the absence of jaundice following the use of gamma globulin in measles.

**Dengue**—The general view is that there is little danger of introducing into this country, through soldiers returning from fighting fronts in the tropics, strains of dengue virus more virulent than the mild form endemic in some Gulf states. Sabin and Schlesinger<sup>45</sup> record one more step toward the achievement of a prophylactic vaccine against dengue in their demonstration that the mouse-passaged virus with which they have been working is indeed dengue, since its injection into human volunteers produced the disease. They note the rapidity with which dengue spread from one

island to another, in one Pacific epidemic, and its final appearance in Hawaii, in which it had not been known before in epidemic form.

**DDT** has once more demonstrated its value in the control of insect-borne diseases: During the taking of Saipan, plane-spread DDT was effective, with improved sanitary measures, in controlling the rapid spread of an epidemic of dengue among our troops.<sup>64</sup>

### Spirochetal Infections

**Syphilis**—The age-long search for effective chemical treatment of syphilis—involving the exploration of mercury, the arsenic-heavy metals, penicillin—cannot yet be said to have ended.

*Status of Heavy Metal Therapy*—Since the reinvestigation of the value of massive doses of **arsenicals**, given over a short period of time, begun in this country in 1933, the method has been tried in a number of clinics. A final evaluation of the method as carried out by 22 cooperating clinics published in 1944 by the United States Public Health Service analyzed 4351 intensive treatments completed in 5 or 6 days. Although one method, arsenicals injected by the multiple syringe technic combined with bismuth and artificial fever, is reported to have produced 85 to 90 per cent cures in early syphilis, and 70 per cent cures in secondary syphilis, the toxic manifestations were serious. Moore,<sup>15</sup> summing up the result of the work of the Cooperative Clinical Group, observes,

"... as late as June, 1943—only a short seventeen months ago—there was still disagreement among doctors as to the best manner of treating even the simplest form of syphilitic infection, the acute early stages of the disease."

A. B. Cannon, in the previous year, had had no hesitation, after treating 332 cases of early syphilis by the massive

technic, compressed into 5 to 6 days, in disposing of the treatment as "ineffective, dangerous, expensive, and altogether impractical." With regard to the most effective period into which treatment can be compressed, Moore,<sup>15</sup> commenting upon Eagle's evaluation of the treatment of 4823 cases of early and latent syphilis, emphasizes the point that the lengthening of the treatment period, from 10 days or less to from 10 to 12 weeks, reduced the mortality rate from 1:200 to 1:3000. With regard to the comparative efficacy of mapharsen alone, and **mapharsen** combined with **bismuth**, Eagle's evaluation noted that while mapharsen alone gave a poor response, triweekly injections of 1 mg. of mapharsen per kilogram when combined with 0.2 gm. of bismuth gave a good response in over 80 per cent, with 82 per cent showing a good response in a nine-week treatment period, and 85 to 90 per cent showing a good response when the treatment period was prolonged from nine to twelve weeks. A modification of this schedule (with more bismuth and a treatment period shortened to twenty days) was put into effect by one group of medical officers of the United States Army in the European theater of operations.<sup>16</sup> In the 435 cases followed for four months or longer, the authors judged the results to be equal to those from more prolonged methods. The Army's rapid treatment (bismuth-mapharsen) extends over twenty-six weeks.

*Penicillin*—The announcement a few years ago by Mahoney, Arnold, and Harris that penicillin appeared to cure primary syphilis in rabbits and man has naturally been followed by further intensive investigation. The clinical trial of penicillin in syphilis has, during the war years, been going forward in some twenty-five civilian clinics and in Army, Navy, and Public Health Service estab-



lishments with the cooperation of the Office of Scientific Research and Development and under the general auspices of the Penicillin Panel appointed by the Subcommittee on Venereal Diseases of the National Research Council. A few reports of clinical investigations are beginning to appear. Since early syphilis and neurosyphilis constitute major problems in the armed forces and, since results of the treatment in these conditions are more easily assessed than those in late syphilis, the first studies have dealt with these aspects of the infection.<sup>15</sup> Among these studies, an analysis<sup>17</sup> of six cases of syphilis resistant to *arsenic-bismuth* treatment (cases of early syphilis with psoriasiform lesions) notes sterile lesions in from ten to twenty-six hours. The injections were given at intervals of from three to four hours day and night for eight days, and consisted of 2,400,000 units in 60 mg. of 40,000 units each. Another study<sup>18</sup> of 106 cases of symptomatic neurosyphilis, 70 of which were followed from 4 to 12 months after therapy, showed improvement in 28 cases, no change in 37, a worsening of the condition in 5, the greatest improvement being noted in 49 with general paresis. No striking difference, however, was noted between these results and those achieved by older methods. In this case, the *penicillin injections* were given 3 hours apart, 300,000 units in 60 intramuscular injections, with *fever therapy*.

The results of penicillin therapy in early syphilis seem to have the unqualified approval of the workers concerned. Of its use in late syphilis, Stokes<sup>19</sup> observes that while penicillin appears to achieve almost miraculous results, the mechanism of its action is not understood:

"... Penicillin, as sodium salt of an as yet incompletely analyzed and understood sub-

stance, is an effective therapeutic agent in the treatment of late syphilis. Under conditions not yet clearly defined, it produces transformations symptomatically and serologically without reaction, or even serious inconvenience to the patient, which are equal if not superior to those obtained by long and arduous procedures involving arsenicals and heavy metals."

Solomon and his associates<sup>18</sup> believe that the time has not yet arrived for the general use of penicillin in neurosyphilis. Other workers,<sup>20</sup> observing that there have been no available reports concerning the use of penicillin in cardiovascular syphilis, report that they were forced to discontinue therapy in two patients with syphilitic aortitis because of untoward effects.

The chief disadvantage of the concentrated treatment of syphilis with penicillin as noted by investigators is the necessity for intramuscular injections at frequent intervals night and day. In the natural effort to meet this difficulty, there have been developed during the past few years, for instance, by Roman-sky and his colleagues, suspensions of penicillin in substances that prolonged markedly the therapeutic blood concentration of penicillin. Peanut oil, sesame oil, cottonseed oil, castor oil, and protamin zinc all affected a prolongation of action of penicillin. The best results were obtained with a mixture of peanut oil and beeswax. More recently, investigators at Cornell<sup>21</sup> have tested various inhibitors of absorption in relation to the prolongation of action of penicillin. They set an arbitrary standard of serum concentration of 0.078 unit per cc. The beeswax suspensions gave the best results in their experience. Office treatment of syphilis by penicillin must obviously await the demonstrated success of these efforts to prolong its action.

Herrell<sup>22</sup> and other workers in the penicillin therapy of syphilis warn that sufficient time has not elapsed for a

genuine evaluation or for an appreciation of the complex factors involved. Moore<sup>15</sup> stresses the need of taking deeply into account all the puzzling questions that involve "the time-dose relationship," the route of administration, the need of combining penicillin with other drugs, or other nonspecific methods of treatment.

*Serodiagnosis of Syphilis*—The challenging problem caused by the familiar false positive reactions in the complement fixation test for syphilis acquires greater importance with the increase of mass surveys of population groups to determine the incidence of syphilis. While it is known that malaria, leprosy, tuberculosis, some virus infections, etc., do sometimes produce false positive reactions, the rate of these reactions is not known.<sup>23</sup> An extensive series of investigations aiming at the discovery of means for differentiating false positive and true syphilitic sera, initiated by Eagle and his colleagues<sup>23</sup> was inconclusive: It was not found possible to make a true distinction in a single instance. The same objective has led to attempted purification of syphilitic antibody and its study by methods of protein chemistry. Investigators at the Neurological Institute, Columbia University,<sup>24</sup> obtained the antibody protein dissociated from specific floccules. Ultracentrifugal analysis showed that the antibody was associated with both a light and a heavy globulin component. Electrophoresis, ultracentrifugation, and purification failed to show any significant differences between a number of syphilitic and false positive sera. Nonspecific methods were also tried by investigators at Duke University.<sup>25</sup> These included studies of true syphilitic and false positive sera by electrophoretic analysis, fractionation, inhibition, and redispersion, differential inactivation by

heat, and adsorption on Ca phosphate. Differences obtained are looked upon as significant with regard to the possibility of developing a practical method of differentiation.

*Yaws*—Illustrative of current trials of *penicillin* in yaws is the trial in a small Army series<sup>26</sup> in which penicillin is reported to have caused a disappearance of *Treponema pertenue* from cutaneous lesions in seventeen cases of primary and secondary yaws, the organism disappearing within sixteen hours in sixteen cases, and within forty hours in the seventeenth.

*Leptospirosis Icterohemorrhagica (Weil's Disease)*—The effectiveness of penicillin in syphilitic infections has led naturally to the investigation of its effect on Weil's disease, the mortality from which in human infections has been estimated as between 10 and 48 per cent.<sup>22,27</sup> Studies of the effect of penicillin on experimental infections suggest a notable reduction in mortality rate, with indications that the value of *penicillin* in the experimental disease in animals depended upon administration very soon after the infective dose.

### Protozoan Infections

*Malaria*—Unquestionably the mortality rate in malaria within the United States has tended to decrease. Faust, Scott, and McDaniel<sup>28</sup> have assembled figures that show great progress in the control of malaria in the United States during the years from 1940 to 1943. The same workers show, on the basis of figures from forty-seven states, that at least a 1 per cent incidence of malaria prevails throughout a considerable proportion of the South—an incidence, roughly, of 300,000 out of an estimated population of 30,000,000. These workers refer to a chart issued by the Office of the Surgeon General of the United States Army

indicating that the malaria admission rates for home troops has been considerably less than 1 per 1000 since early 1942, "while that for the entire Army overseas has fluctuated essentially under 50 per 1000, except for the year 1943 when it climbed for a time to slightly over 150."<sup>28</sup> In spite of this evidence of decrease on all fronts, Faust and others hold the view that so long as the returning men harbor the gametocyte stage of the parasite and so long as *Anopheles* mosquitoes have access to these malaria cases, so long does it remain possible that tropical strains of the disease could become established in this country. As to how serious this hazard is, opinion is divided. The Committee on Epidemiology of the National Malaria Society,<sup>29</sup> expressed, in the current year, its view that the importation of malaria strains is not likely to have a marked effect on the current downward trend of malaria in this country, "although its influence may be felt for several years after demobilization."

There is no doubt that most of the returning individuals with relapsing malaria will be infected with *P. vivax*. This is based upon the established fact that *atabrine*, which has been extensively and regularly used in suppressive treatment, destroys the relatively short-lived *P. falciparum*.<sup>29, 30</sup>

On the two possible lines of attack, a direct attack on the human plasmodia by chemotherapy, and an indirect attack through control of mosquito vectors: Bradley, of the Public Health Service, believes that, although the attack on the parasite in the human host is the most logical, the fact that no chemotherapeutic or immunological agent has yet been found that will prevent infection or kill the parasites *in vivo* makes control through the eradication of mosquito vectors more promising.<sup>31</sup> On the other

hand, the committee of the National Research Council, representing the cooperation of the Army, Navy, United States Public Health Service, and the Office of Scientific Research and Development, responsible for the direction of work on malaria control, agreed that

"... an attempt to control malaria through the vectors was a long-time project, and that the immediate attack on malaria control will have to be with chemotherapeutic agents."

This line of attack was put into effect by the Board for the Coordination of Malarial Studies, a joint body composed of representatives of the Army, Navy, Public Health Service, Office of Scientific Research and Development, and the National Research Council, by setting up four subcommittees (Panel on Syntheses, Panel on Biochemistry, Panel on Pharmacology, Panel on Clinical Testing), each with large groups of outstanding scientists, for the production and clinical testing of antimalarials.

A practical course that should be followed by physicians faced with the problem of malaria in returned Army personnel was outlined several years ago by Sawyer of the International Health Division of the Rockefeller Foundation, who stressed the need of definite procedures to assure the use of existing knowledge by medical practitioners generally. One of his recommendations is that the malaria patient, on discharge from a military hospital, should be notified in writing of the diagnosis and the species of plasmodium involved and should be instructed to consult a physician and show him the communication on the occasion of any subsequent illness within a year. Distinctly in order in this connection is the detailed information published in Circular Letter No. 153, from the Office of the Surgeon General of the Army, dated August 19, 1943,

and War Department Medical Technical Bulletin No. 56, dated July 3, 1944.

Facilitation of the diagnosis of malaria has been the objective of two lines of work. Metcalf and his co-workers<sup>32</sup> have applied fluorescent microscopy to the examination of blood smears for plasmodia, using fluorescent dyes as histological stains. The smears are then irradiated by ultraviolet rays which produce, in effect, a light source in the microscopic object itself. This produces a dark field in which the parasites appear as luminous bodies within the dark outlines of erythrocytes, recognizable even in a rapid scrutiny of the slide.

Other investigators are continuing efforts to produce an effective antigen for complement fixation tests for diagnosing malaria. Heidelberger and his associates have prepared an antigen from *P. gallinaceum*. Recently they have found that many human malarial sera which fail to react with this antigen fix complement strongly with an antigen prepared from normal human stromata. This reaction is, in effect, reasonably disease-specific for malaria, since in thirty-two normal and eighty-one pathological sera, only four probable false positive reactions were found in the latter group. In patients with chronically relapsing vivax malaria, the normal human stromata antigen is as sensitive as the gallinaceum antigen and is prepared more easily.

*Drugs in Malaria*—The outstanding positive advance in the drug treatment of malaria during the war years has been the wide experience gained in suppressive treatment with *quinine* and *atabrine* (*quinacrine*). The sharp limitation of the supplies of quinine has made atabrine an enforced choice. This, however, according to McCoy,<sup>33</sup> has been an advantage, for

"Atabrine has proved much more effective than quinine for suppression of malaria and, in general, is better tolerated and preferred by troops."

So far as is known, the administration of small suppressive doses can be continued indefinitely without ill effects but the requirement varies among individuals and at different times in the same individual. Experimental work with atabrine and the extensive experience with its clinical use during the war years have, according to Shannon and Earle,<sup>55</sup> established that "its antimalarial activity at any time is a simple reflection of its concentration in the plasma." Initial doses of the drug, according to them, must be high enough to insure a high initial plasma drug concentration and an abrupt therapeutic effect. The best therapeutic effect is gained from a plasma drug level of 30 mg. per 1000 cc. maintained for four days or more. For all but the exceptional individual, the recommended dosage schedule is, according to these authors:

"... 0.2 gm. doses of quinacrine . . . given at the time of the diagnosis of malaria, and at four-hour intervals until a total of 1.0 gm. has been given. Thereafter, it should be continued at a dosage level of 0.1 gm. three times daily for a total period of seven days."

The work on drugs conducted under the sponsorship of the Committee on Medical Research of the Office of Scientific Research and Development has been extensive, involving many laboratories and clinics, but war policy restricting publication of the results of these studies is still operative. As a part of this work, approximately 1200 compounds were studied at the University of Michigan School of Public Health during 1944 for curative or prophylactic action in experimental malaria. Investigators in the Laboratories of the International Health Division of the Rockefeller Foun-

dation have cooperated with investigators working under Fieser in the Harvard chemistry department in a study of a series of compounds entirely different from the known antimalarial drugs. Some of the new series of synthetic compounds demonstrated to be highly effective in avian malaria have been disappointing in trials on human malaria because the compounds apparently suffer metabolic degradation to a greater extent than in the test animal. These findings led to further studies on the metabolism of other compounds of the series in human subjects and thus to a means of discovering compounds superior to those first tried.

The use of *plasmochin* for therapy and suppressive treatment has given evidence of dangerous toxicity. According to recent reports of Army experience, the drug is not safe for use either in the field or in hospitalized patients. Clark, director of the Gorgas Memorial Laboratory in Panama, found in 1944 that the usual dose of 0.01 gm. three times a day for five days produced toxic effects in one out of ten patients. He also believes that no benefit was derived from its use as a gametocide or as a suppressive in the field. Two members of the United States Army Medical Department in the same year note that of 846 cases hospitalized for falciparum malaria and treated with the same dose of plasmochin, twenty-four had to be readmitted, suffering from toxic effects. They regard the individual reaction to plasmochin as inconsistent and unpredictable and convalescence from toxemia as slow.

If a specific drug that will actually cure or prevent malaria has been discovered, it has not yet been announced. As an evaluation of the present status of antimalarial drugs, the special report published in the spring of 1945 by the

Board for the Coordination of Malarial Studies, is pertinent:

"While quinine and atabrine (quinacrine) are very efficacious drugs in suppressing the clinical attacks of vivax malaria, neither is capable of eradicating the disease completely once a person has become infected. . . .

"The large number of men returned to the United States with recurring attacks of this type of malaria attests the incomplete worth of available drugs against this disease. . . ."

*Prophylactic Vaccine*—Work on anti-malarial vaccines is going forward in several centers but in the absence of human tests, the use of antimalarial vaccines with various adjuvants in ducks and monkeys<sup>56</sup> does not, as yet, change the conclusion reached a few years ago by Coggeshall:

"The acquisition of immunity following the inoculation of killed malarial organisms is only demonstrable under exceptional conditions. . . ."

### Danger of Importation of Other Parasitic Infections

There are naturally no reliable estimates (and opinion is divided) as to the degree to which the return of the military personnel from tropical areas, and increased traffic with these areas, will result in a mounting incidence of parasitic diseases (protozoan, metazoan, mycotic), already known in this country, as amebiasis, or in the introduction of infections not previously found in the civilian population, or occurring only in occasional and limited instances. The most recent research projects developed by the Committee on Wartime Tropical Medicine, of the National Research Council, according to Meleney,<sup>37</sup> have especially dealt with leishmaniasis, amebiasis, and, of the helminthic infestations, filariasis and schistosomiasis. Preventive efforts look largely to the only prophylactic measure now practicable, control of vectors, *e. g.*, the elimination of mosquitoes from areas where indi-

viduals returning to this country infected with filariasis might serve as a reservoir of infection; study of domestic snails as possible vectors of schistosomiasis; study of domestic species of *Phlebotomus* (sand flies) as possible vectors of leishmaniasis. With reference to the tsetse fly, responsible for the transmission of the trypanosomes gambiense and rhodesiense, which cause "African sleeping sickness," and of the blood-sucking cone-nosed bug responsible for the transmission of the *Trypanosoma cruzi*, causing Chagas' disease, Sawyer recommends disinsection of airplanes and ships for an indefinite time in the postwar period to prevent introduction of these insects into the western hemisphere.

The mycotic infections often met in fulminating form in tropical areas during the war years are regarded as nearly all world wide in their distribution. Under the auspices of the National Research Council, investigators at the Duke University Medical School have prepared a *Manual of Clinical Mycology*, covering the pathological processes caused by the pathogenic fungi, and emphasizing the need of considering the possibility of fungi in the differential diagnosis of "practically every obscure infection."<sup>66</sup>

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## CARDIOVASCULAR SYSTEM

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### Coronary Artery Disease

**Relationship of Effort to Acute Myocardial Infarction**—The question of the relationship of effort to acute myocardial infarction is of considerable importance in diagnosis as well as in proper clinical management. Legal decisions in civilian life and the line of duty determination in military service are often vitally affected. From observations in many Army hospitals, it is the opinion of Blumgart<sup>1</sup> that a causal relationship exists between strenuous effort and attacks of acute myocardial infarction. Most military personnel are called upon to undertake strenuous effort and, particularly in the case of some officers from civilian life, such effort is often decidedly unaccustomed. The incidence of acute myocardial infarction in the Army has been notable, and in many instances there

has been a definite history of unusual physical exertion a short time beforehand.

The clinical criteria which must be satisfied to demonstrate a relationship between strenuous effort and myocardial infarction are (a) the development and increase of cardiac symptoms, such as pain or substernal distress during or immediately following unusual effort; (b) continuation of the symptoms after cessation of effort; (c) presence of clinical signs and symptoms of acute myocardial infarction, and (d) the development of a characteristic electrocardiographic pattern of acute anterior, posterior, or lateral wall myocardial infarction.

The pathologic mechanisms which induce acute myocardial infarction during or soon after effort are (a) subintimal hemorrhages or the rupture of an ather-

omatous abscess following strenuous effort and (b) the occurrence of relative ischemia brought about by strenuous effort and resulting in a need for increased blood flow which the arteriosclerotic vessels are unable to meet. An artery narrowed by arteriosclerotic changes may transmit sufficient blood for the ordinary needs of the myocardium but may not be competent to transmit the increased blood flow required by the heart during effort. Under such circumstances the heart muscle suffers from relative ischemia, and if this is sufficiently prolonged, irreversible damage, *i. e.*, infarction, results. Sudden death may be due to development of ventricular fibrillation or cardiac standstill because of myocardial ischemia in the absence of any fresh pathologic changes in the coronary arteries.

Subintimal hemorrhages are not believed to occur in a normal artery but take place only in an atheromatous lesion. Intimal capillaries, since they arise directly from the lumen, are more liable to rupture in the presence of softening due to an atheromatous lesion which allows the transient increased pressure of blood within the capillary attendant to exertion or emotion to dilate its walls to the extent of rupture. The fragility of the capillary wall may also be affected by anoxemia, by the presence of local or general toxic factors and by impaired nutrition. The formation of a hematoma within the wall of an artery may raise the intima and occlude the lumen partially or completely; in some instances, the hemorrhage may rupture the intima, exposing an open hemorrhagic wound, which constitutes a favorable site for the development of a thrombus. Subintimal hemorrhage and subsequent thrombus formation may develop gradually over a period of days or even a week or two and serve to explain some cases in which

an appreciable interval separates the strenuous activity from the acute attack.

Appreciation of the importance of effort or excitement as a precipitating factor in angina pectoris or acute myocardial infarction should prompt direct inquiry regarding all attendant circumstances prior to the onset of the attack. The appearance of distress on exertion or under emotional stress should indicate a tentative diagnosis of angina pectoris, coronary failure, or insufficiency, or myocardial infarction until such a diagnosis is excluded on the basis of further evidence. Aside from physical effort and emotional stress, other factors, such as the ingestion of food or exposure to cold, which increase the work of the heart, may be of etiologic importance. If several days intervene between physical effort or other possible etiologic factors and the development of acute myocardial infarction, the relationship cannot be considered definite unless there is a continuity of symptoms bridging the interval.

**Anoxia Test in Coronary Insufficiency**—In a study by Pruitt, Burchell, and Barnes<sup>2</sup> of 282 patients at the Mayo Clinic, each of whom presented some clinical evidence of angina pectoris (although in most instances this diagnosis could not have been made on the basis of clinical evidence alone), the results of the anoxia test, performed according to the method established by Levy, were electrocardiographically positive in 71 cases (25 per cent). Seven healthy men with no history suggestive of angina pectoris were used as controls; and none of them showed significant electrocardiographic changes or experienced pain during the anoxia test.

The test was performed under basal conditions. It was never performed in the presence of congestive heart failure or within four months after a suspected



cardiac infarction or more than once in twenty-four hours in the same case. By means of a reservoir bag and a mask, the patient breathed 10 per cent oxygen and 90 per cent nitrogen. A tank containing 100 per cent oxygen was included in the apparatus, and a flood valve permitted almost instantaneous replacement of the 10 per cent oxygen mixture by 100 per

cent oxygen; in 29.9 per cent, the results of the test were completely negative, and in 3.3 per cent, the test was unsatisfactory. Of 108 cases with an equivocal history of angina pectoris, the test was electrocardiographically positive in 19.5 per cent; in 18.5 per cent, pain was occasioned during the test but there were no significant electrocardiographic

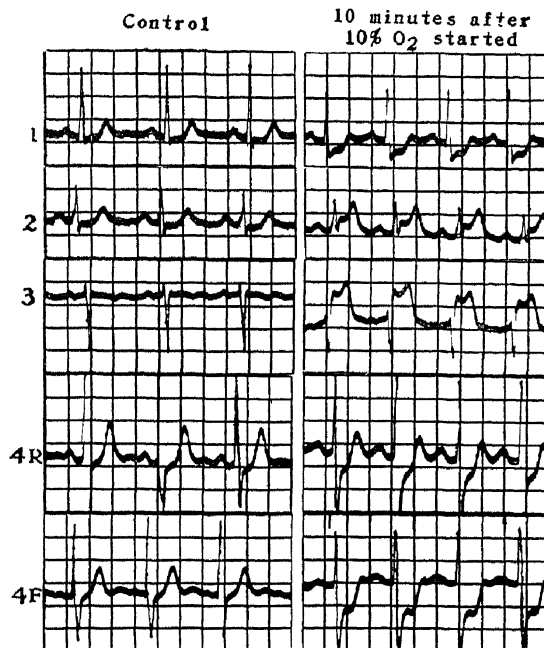


Fig. 1—The patient was a man aged 38. Six days prior to examination recurring episodes of pain in the chest suggestive of severe coronary insufficiency had occurred. The routine electrocardiogram did not afford satisfactory evidence of recent infarction. Seven minutes after inhalation of the mixture of 10 per cent oxygen and 90 per cent nitrogen was begun the patient complained of slight pain in the left elbow. The electrocardiogram taken ten minutes after the test was begun is of particular interest because the changes recorded simulate those associated with acute infarction of the posterior portion of the left ventricle.

cent oxygen. The usual period of observation was twenty minutes. On completion of the test, 100 per cent oxygen was given for from one to two minutes, a time adequate for the subsidence of cyanosis.

Of ninety-two cases in which a history highly suggestive of angina pectoris was obtained, the test was electrocardiographically positive in 53.2 per cent; in 19.6 per cent, pain was experienced but there were no significant electrocardio-

graphic changes; in 50 per cent, the results of the test were completely negative; and in 12 per cent the test was unsatisfactory. Of eighty-two cases with few if any suggestions of a true anginal syndrome, the test was electrocardiographically positive in 1.2 per cent; in 11 per cent, pain occurred but there were no significant electrocardiographic changes; in 76.8 per cent, the results of the test were completely negative; and in 11 per cent the test was unsatisfactory.

In the majority of instances (66.2 per cent) in which the test was electrocardiographically positive, the only significant change consisted of a deviation, usually a depression, of the RS-T segment, totaling 3 mm. or more, in leads I, II, III, and IVF. While depression of the RS-T segment, especially in leads IVF and IVR, was the commonest type of change in the positive test, striking elevation of this segment occurred in four cases. In three of these, elevation of the RS-T segment was most pronounced in lead III and was accompanied by segmental depression in lead I (Fig. 5). Slight increase in height or decrease in negativity of the T wave in lead IVF or IVR is believed to be associated more frequently with a history suggestive of angina pectoris than is a depression to the isoelectric or diphasic level of a positive T-wave in these leads. Significant changes occurred in lead IVF and not in lead IVR in only two tests, and in lead IVR and not in lead IVF in only four tests.

Twenty-five of the 289 tests were regarded as unsatisfactory because of unfavorable reactions. Nine patients had vasovagal reactions characterized by a fall in blood pressure associated with slowing of the pulse rate and, in some instances, with cold sweat, pasty color, and the appearance commonly seen in shock. In three instances, the test was discontinued because of nausea, and in four other cases it was discontinued because of severe generalized discomfort or a request that the procedure be interrupted. Loss of consciousness occurred in three cases. In five cases the number of premature contractions increased during the test, and in eight additional cases this type of arrhythmia persisted unchanged throughout the period of oxygen want. Nodal rhythm developed during the test in two cases. In two cases there

TABLE I

COMPARISON OF MORTALITY IN CASES IN WHICH AURICULAR FIBRILLATION DISAPPEARED AND IN THOSE IN WHICH IT PERSISTED

	Mortality (%)
1,247 (whole group) . . . . .	51.5
84 (with auricular fibrillation) . . . . .	79.8
29 (in which arrhythmia disappeared) . . . . .	58.6
55 (in which arrhythmia persisted) . . . . .	89.4

was complete cardiac arrest, which in one case lasted for more than three seconds and in the other for exactly four seconds.

The authors conclude that the anoxia test is not a laboratory short cut to the diagnosis of coronary sclerosis but is a means of substantiating a diagnosis of angina pectoris based on fairly convincing clinical evidence. Negative results should not be accepted as evidence of adequate coronary circulation. Use of the test should be restricted to cases in which (1) serious disagreement regarding diagnosis has occurred and (2) the establishment of a definite diagnosis is of such importance that acquisition of all helpful evidence is imperative.

**Treatment of Auricular Fibrillation Occurring with Myocardial Infarction**—In a study of eighty-four patients, made by Askey and Neurath<sup>3</sup> at the Los Angeles County General Hospital, auricular fibrillation in association with myocardial infarction has been found to be a hazard in regard to both the incidence of systemic arterial emboli and the mortality rate. The eighty-four patients represented an incidence of auricular fibrillation of 7.7 per cent among 1247 patients with myocardial infarction admitted to the hospital. The mortality among the 1247

TABLE II  
RELATION OF TIME OF DEVELOPMENT OF  
AURICULAR FIBRILLATION TO THE DISAP-  
PEARANCE OR PERSISTENCE OF THE  
ARRHYTHMIA

Relation to Time of Myocardial Infarction	Auricular Fibrillation		Mor- tality
	Dis- appeared	Per- sisted	
8 (preceded) . . .	1	7	99.0
41 (coincident) .	1	40	81.8
35 (followed) . . .	27	8	72.0

patients with myocardial infarction during their hospitalization (about one month) was 642, a rate of 51.5 per cent, whereas the 84 patients with auricular fibrillation had a death rate of 79.8 per cent (Table I).

In the group of twenty-nine cases in which auricular fibrillation disappeared, the mortality rate was 58.6 per cent, whereas in the fifty-five cases in which it persisted the death rate was markedly increased (89.4 per cent). The worst prognosis was among those in which auricular fibrillation was known to have existed before myocardial infarction (99 per cent mortality, with 57 per cent dying of systemic arterial embolism) (Table II), and among those who had had a previous myocardial infarction (96

per cent mortality, with 30 per cent systemic embolism) (Table III). In nearly all cases in which the auricular fibrillation preceded or coincided with the onset of the myocardial infarction, the arrhythmia persisted, whereas in nearly three fourths of those in which the auricular fibrillation occurred after myocardial infarction, the arrhythmia disappeared. The group with persistent auricular fibrillation showed evidence of marked preexisting cardiac damage. Nearly one third of the deaths in this group were due to systemic arterial emboli, in contrast to only one ninth in the group in which the arrhythmia disappeared. The conversion to sinus rhythm was not as productive of emboli as was the persistence of the arrhythmia.

Although auricular fibrillation tended to disappear in the majority of patients who received *quinidine* alone, and to persist in the majority of patients who received *digitalis* alone, the effect of the medication was not conclusive. Quinidine alone was used for patients with little preexisting heart damage, in many of whom the arrhythmia was recent and might have disappeared spontaneously, whereas digitalis alone was used for those with marked preexisting damage, in many of whom the arrhythmia was already established. It is impos-

TABLE III  
COMPARISON OF PERSISTENT GROUP WITH TRANSIENT GROUP

Auricular Fibrillation	Aver- age Age (Yrs.)	Previous Cardio- Vascular Disease	Previous Infarcts	Congestive Failure	Systemic Emboli	Deaths
Transient . . . (29)	66	12 (41.3%)	2 (6.9%)	7 (24%)	2 (11%) (of deaths)	17 (58.6%)
Persistent . . . (55)	68	46 (83.6%)	30 (52.6%)	41 (71.8%)	15 (29.4%) (of deaths)	51 (89.4%)

TABLE IV

TYPE OF DEATH OF 48 PATIENTS WITH CONGESTIVE FAILURE AND AURICULAR FIBRILLATION  
COMPLICATING MYOCARDIAL INFARCTION

	32 Patients Receiving Digitalis Alone	8 Pa- tients Receiving No Digoxin	Patients Receiving Quinidine and Digitalis	1 Patient Receiving Quinidine Alone
Systemic embolism (cerebral or peripheral vessels)	13	0	0	0
Pulmonary embolism.....	3	0	1	0
Acute congestive failure (both ventricles)	4	1	1	1
Acute left ventricular failure.....	3	1	2	0
Sudden death.....	0	3	0	0
Pneumonia.....	1	0	0	0
Rupture of heart.....	1	1	0	0
Lived.....	1	2	3	0
Total.....	32	8	7	1
Return to sinus rhythm.....	3	0	5	1
Mortality.....	96.8%	75%	57.1%	100%

sible to predict, therefore, whether or not auricular fibrillation would have disappeared anyway in those cases in which quinidine apparently stopped it. It is also impossible to predict what the effect upon the arrhythmia would have been had quinidine been given in addition to digitalis in those cases in which the auricular fibrillation persisted.

Digitalis administered alone to thirty-two patients with manifestations of congestive myocardial failure was found to be more harmful than beneficial, the mortality rate being 96.8 per cent (Table IV).<sup>4</sup> Clinically recognized fatal embolism in the greater circulation occurred in thirteen of the thirty-one patients who died; whereas none of the sixteen patients receiving other treatment had fatal embolism in the systemic circulation. In the group of thirty-six patients without congestive failure, digitalis alone produced no greater incidence of systemic embolism than did other types of treatment. Sudden death from fatal ectopic ventricular rhythm or car-

diac rupture was no greater hazard after the administration of digitalis than with other therapy. In most cases, digitalization was fairly rapid, averaging 1.5 to 2 gm. (24 to 30 grains) of the powdered leaf in three to four days.

The importance of preexisting mural thrombi in producing embolism, and particularly the importance of the duration of auricular fibrillation in producing the thrombi, was suggested by the high incidence of fatal emboli in the group of eight cases in which the arrhythmia was present before the onset of myocardial infarction. Of the seven who died, five (71 per cent) died of emboli in the greater circulation. The effect of old age in relation to mural thrombi was evidenced by the fact that the average age in this group was seventy years. Persistence of auricular fibrillation tends to produce new auricular thrombi and to augment old thrombi. And the administration of *digitalis* ordinarily tends to fix and perpetuate the arrhythmia. Increase of the blood coagulability by digi-

TABLE V

RESULTS OF MEDICATION IN THIRTY-SIX PATIENTS WITH MYOCARDIAL INFARCTION AND AURICULAR FIBRILLATION BUT NO CONGESTIVE FAILURE

	Number	Auricular Fibrillation Stopped	Percentage Returned to Sinus Rhythm	Number Systemic Emboli	Number Died	Mortality (%)	Sudden Death (%)
Digitalis and quinidine . . . . .	5	4	80	1	4	80	0
No medication . . . . .	9	5	55	2	6	66.6	1 (16)
Digitalis alone . . . . .	12	3	25	1	9	75	1 (11)
Quinidine alone . . . . .	10	8	80	0	5	50	3 (60)
Total . . . . .	36	8	55	4	24	66	

talis also may be a factor in increasing the number of intracardiac thrombi. In addition, the effect of digitalis on the enlarged heart, *viz.*, the production of a slower stronger systole with a reduction in the size of the ventricular cavity, may dislodge and expel a ventricular thrombus.

In the group of patients without congestive failure, *quinidine* alone gave better results than no medication or digitalis alone (Table V).<sup>5</sup> In this group digitalis alone was harmful apparently because it prevented a spontaneous return to sinus rhythm. Quinidine alone was harmful only when given in the presence of obvious conduction defects. Although sudden death occurred if no medication was given, or if digitalis alone or quinidine alone was given, it occurred in none of the twelve patients given both digitalis and quinidine.

In the group with congestive failure, the best results were obtained from combined digitalis and quinidine administration. In this group there was the lowest mortality, the greatest percentage of return to sinus rhythm, and no sudden deaths from embolism.

The practical problem of treatment in the entire group of eighty-four patients was the treatment of the forty-nine cases in which auricular fibrillation developed coincident with the attack. Only two of

these forty-nine cases reverted to sinus rhythm, and forty-two (85.7 per cent) died; whereas, of thirty-five patients who developed auricular fibrillation after the attack, the arrhythmia persisted in only eight instances. In the absence of congestive failure, it would seem advisable to wait twenty-four hours to determine whether or not the arrhythmia is transient. The group of patients who presented auricular fibrillation in the first electrocardiogram, however, usually had had previous severe cardiovascular disease, and a large percentage had congestive failure. In such cases, treatment directed to the elimination of the arrhythmia as well as to improvement of the ventricular systole should give the best results.

The administration of *quinidine* in congestive failure ordinarily is considered contraindicated, but in congestive failure associated with auricular fibrillation in myocardial infarction it would seem to be indicated since (1) *digitalis* alone has been found to increase rather than decrease the mortality rate; (2) digitalis plus quinidine has proved to be of benefit; and, theoretically, (3) a quick return to sinus rhythm should (a) prevent further auricular thrombus formation and forestall embolism, and (b) reduce the ventricular rate after the

usual initial acceleration. "Theoretically, digitalis and quinidine should act as buffers against each other's action tending to induce an ectopic ventricular rhythm. Digitalis is capable of inducing paroxysmal ventricular tachycardia, an arrhythmia which quinidine can prevent; conversely, digitalis is believed to prevent ventricular tachycardia arising from the use of quinidine in the treatment of auricular fibrillation."

From the findings in this study, it is concluded that in the management of

*quinidine* and *digitalis* should be administered at once. Quinidine should be given every two hours in 0.4-gm. (6-grain) doses if there is no hypersensitivity to an initial 0.2-gm. (3-grain) dose. In such cases the administration of digitalis alone should be avoided. When auricular fibrillation occurs coincidentally with the onset of myocardial infarction, *oxygen* should be given to relieve anoxemia; and *atropine sulfate* in an initial dose of 1.3 mg. ( $\frac{1}{50}$  grain) intravenously and followed by 0.5 mg.

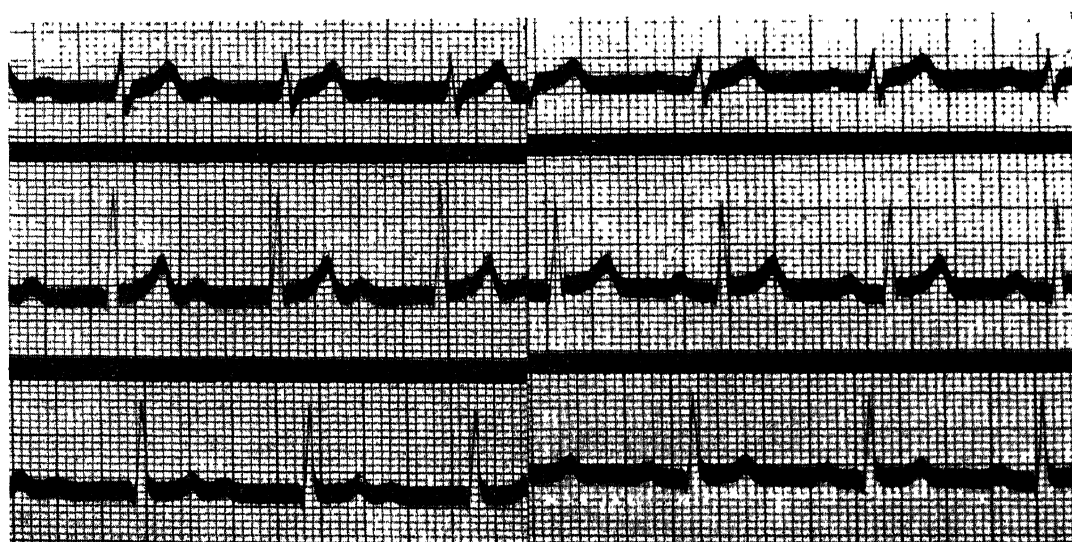


Fig. 2—A, Case 4, 1940. Recumbent; prolonged P-R interval. B, Case 4, 1940. Sitting; normal P-R interval.

auricular fibrillation occurring with myocardial infarction an immediate attempt should be made to eliminate the arrhythmia by the administration of optimum doses of quinidine unless (a) the electrocardiogram shows conduction defects or (b) the arrhythmia develops several days after the onset of myocardial infarction, and congestive failure is not present. In the latter event, twenty-four hours should be allowed to elapse to determine whether there might be a spontaneous return to sinus rhythm. When congestive failure is present, both

( $\frac{1}{120}$  grain) by mouth three times daily may prove of benefit by counteracting reflex vasospasm occurring through the vagus nerves.

### Electrocardiography

**P-R Interval and Change in Posture**—In a study by Manning and Stewart<sup>6</sup> of routine electrocardiograms taken on Royal Canadian Air Force air crew in 1940 and early 1941, 2.2 per cent of the records showed a P-R interval greater than 0.20 second. Further study of twenty men whose original electrocar-

diagrams showed a prolongation of the P-R interval revealed in four instances a definite reduction in the P-R interval on change from the recumbent to the upright position. In one case there was a reduction from 0.28 second in the recumbent position to 0.20 second in the sitting position; in another from 0.24 second to 0.20 second; in a third from

elevating the head of the bed that at 50° from the horizontal, the P-R interval changed to 0.20 second. In the recumbent position, deep inspiration reduced the P-R interval only to 0.36 second. Thirty minutes after the subcutaneous injection of 0.6 mg. ( $\frac{1}{100}$  grain) of *atropine sulfate*, the interval in the recumbent position was still 0.36

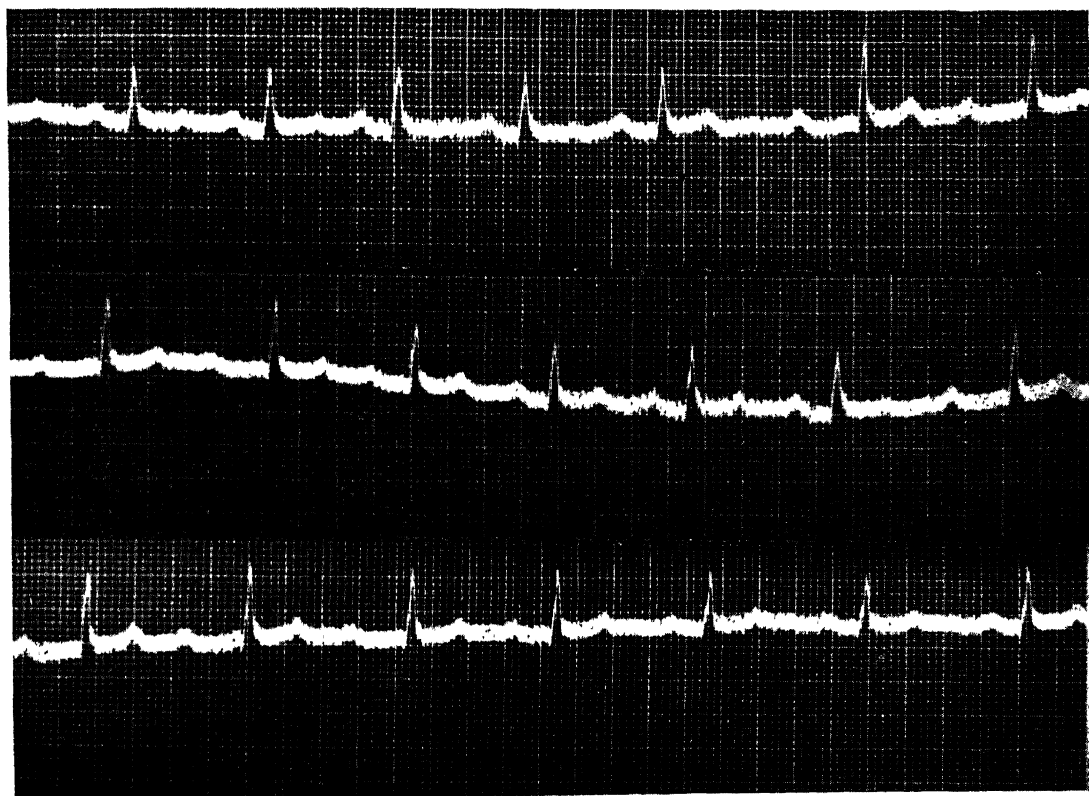


Fig. 3—Case 4, 1944. Lead II, continuous record. Sitting. Top: P-R increased from 0.22 to 0.38 second with deep inspiration. Middle: P-R decreased to 0.24 second on expiration and increased to 0.38 second on forced expiration. Bottom: P-R returned to 0.22 second with normal respiration.

0.24 second to 0.20 second; and in a fourth, a healthy athletic subject, aged twenty-five years, there was a reduction from 0.40 second in the recumbent position to 0.20 second in the sitting position (with little or no change in the heart rate from that in the preceding record [Fig. 2]).

In a study of Case 4, it was found by taking records at various levels by

second. In the right or left lateral or prone position there was a slight increase in the P-R interval beyond 0.40 second accompanied by a slight decrease in the heart rate. An electrocardiogram obtained eighteen months later revealed the same findings with a P-R interval of 0.36 to 0.38 second in the recumbent position; and a record taken three years and nine months after the original trac-

ing revealed a P-R interval of 0.32 second in the recumbent position and 0.16 second in the sitting position, and subcutaneous injection of 1.3 mg. ( $\frac{1}{50}$  grain) of atropine sulfate did not change the P-R interval in either of the two positions. Deep inspiration and deep expiration both prolonged the P-R interval in records taken in the sitting position (Fig. 3), but no significant change was produced by deep breathing in rec-

umbent position, revealed in many instances slight variations in the length of the P-R interval (usually about 0.01 and 0.02 second) and also in the P wave amplitude. In the records of six men, a decrease in P-R interval of 0.02 second accompanied an increase in heart rate produced by change from the recumbent to the sitting position. In one other subject, a P-R interval of 0.18 second and a heart rate of eighty-eight were pre-

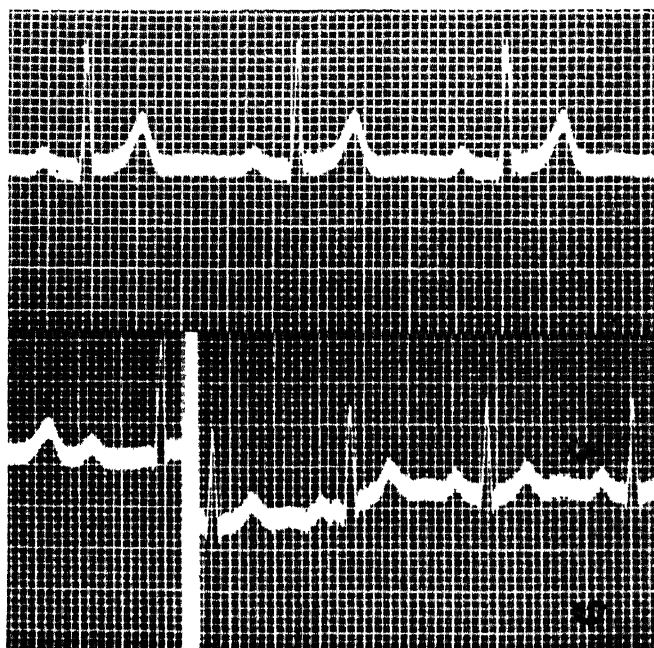


Fig. 4—Case 4, 1944. Recumbent, immediately before and after exercise. P-R interval decreased from 0.36 to 0.18 second.

ords taken in a recumbent position when the P-R interval was already 0.36 to 0.38 second. On exercising the legs for two minutes, as in riding a bicycle, while retaining the recumbent position, the pulse rate was increased to 90, and the P-R was reduced to 0.20 second (Fig. 4).

A study of the electrocardiograms of thirty men with P-R intervals within the range of 0.12 to 0.18 second, taken in the recumbent position and the sitting position during normal respiration, following deep inspiration, and following

deep expiration, revealed in many instances slight variations in the length of the P-R interval (usually about 0.01 and 0.02 second) and also in the P wave amplitude. In the records of six men, a decrease in P-R interval of 0.02 second accompanied an increase in heart rate produced by change from the recumbent to the sitting position. In one other subject, a P-R interval of 0.18 second and a heart rate of eighty-eight were presented in the recumbent position, while in the sitting position the P-R became 0.16 second with no change in heart rate. On deep inspiration in the sitting position, the interval decreased to 0.12 second (which change was in the reverse direction from that observed in Case 4), the heart rate remained practically the same, and there was a marked decrease in the amplitude of the P waves with  $P_{23}$  becoming inverted.

Two possible explanations, *viz.*, an aberrant conduction pathway, or fluctuation in vagal tone (autonomic imbalance),



might be considered for the changes in the P-R interval associated with changes in the posture and respiration and with changes in heart rate produced by exercise. It is possible that the physiologic fluctuations in autonomic balance may be more prominent in these men than in the average individual, and the vagal effects might be so marked that the P-R duration would be increased beyond the accepted normal limits. Why the change

seen to thirty-five years, presenting manifestations of functional derangement of the cardiovascular system, in whom organic heart disease was excluded, it has been found by Wendkos<sup>7</sup> that multiple precordial leads derived from the left hemithorax in recumbency may reveal alterations in the T wave which are indistinguishable from those associated with structural cardiac disease. Distortions in the precordial lead T wave during recum-

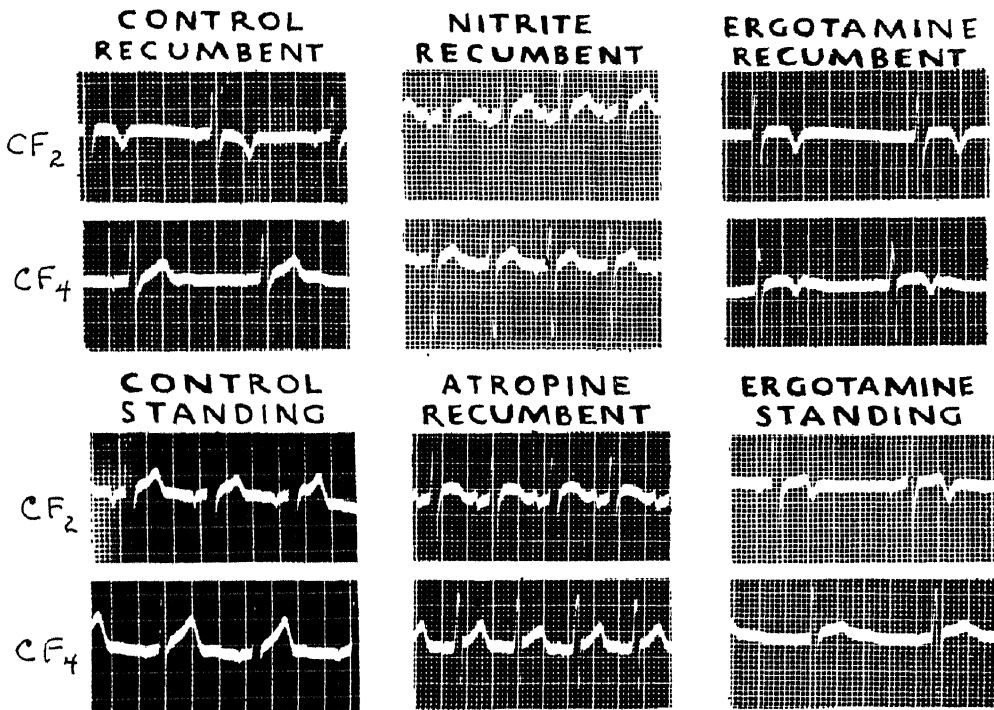


Fig. 5—Case 1.

in posture should be responsible for the production of such effects is not understood.

In view of the fact that marked differences can occur in the electrocardiograms of some individuals with change in posture, it is desirable that the position of the patient during the taking of the electrocardiogram should always be recorded.

**Influence of Autonomic Imbalance on the Electrocardiogram**—In a study of male adults, ranging in age from eight-

bency occurred in 80 per cent of the cases; in one fourth of this number, significant corresponding aberrations of the same deflection occurred in the limb leads in the same record.

Repeated electrocardiograms of one of the cases presented by Wendkos consistently revealed inversion of the T wave in lead  $CF_2$ , without any accompanying T wave changes in the limb leads or in the other chest leads (Fig. 5). The response of the precordial lead T wave to various testing procedures was as

follows: The upright position converted it to a positive deflection. Atropinization, after thirty minutes, independent of any postural change, produced a similar effect, but not to a comparable degree. Amyl nitrite during recumbency produced an effect similar to that brought about by the upright position. Ergotamine, with the patient in the recumbent position, had no significant effect on the inverted T wave in lead  $CF_2$ , but it did convert the positive T wave in lead  $CF_4$  to a negative deflection.

"The characteristic response in this instance of the bizarre T wave in lead  $CF_2$  to sympathomimetic and parasympatholytic influences establishes the fact that it was merely a manifestation of hypervagotonia. The ability of a sympatholytic drug, such as ergotamine, not only to prevent the usual effect of the upright position on the inverted T wave in lead  $CF_2$ , but also to produce T wave distortion in lead  $CF_4$  in the recumbent position, is further evidence in support of this view. The latter experiment, in addition, shows conclusively that any T wave alteration produced by assuming the upright position is to be attributed to increased sympathetic tone, reflexly induced, and not to a change in the position of the heart. Also in favor of this hypothesis are the observations that, in the same case, amyl nitrite, during recumbency, produced T wave changes in both the limb and precordial leads which were indistinguishable from those resulting from a change in direction of the long axis of the body, and that the upright position did not produce polarity changes in the T waves of the limb leads when tachycardia did not occur. On the contrary, the reversal of the vagotonic inverted T wave in lead  $CF_2$  to positive polarity as the result of postural change bore no relation to the heart rate, indicating the functional instability of such

functionally bizarre precordial lead T waves. . . . The inversion of the T wave in lead  $CF_4$  caused by a sympatholytic drug was associated with a heart rate no slower than that concurrent with a normal T wave in the same lead in a control tracing on a different occasion, and the positive T wave in lead  $CF_2$  resulting from assumption of the upright position was not associated with a heart rate any more rapid than that which accompanied an inverted T wave in the same lead in a control record obtained at another time in the recumbent position."

In view of the fact that changes in the precordial T waves with a resemblance to abnormalities which result from structural cardiac disease may be due to preponderance of either vagal or sympathetic tone, the interpretation of any distortion of a precordial lead T wave, especially in cases in which the symptoms or signs are merely suggestive of the presence of organic heart disease, must ultimately depend on a proper assay of these factors. By the testing methods described, it is possible to attribute to vagotonic influences any aberration of the precordial lead T wave which is exaggerated by a sympatholytic drug (such as ergotamine tartrate) and abolished by a parasympatholytic drug (such as atropine sulfate—twenty to sixty minutes after its administration) and a sympathomimetic drug (such as amyl nitrite) or by the assumption of the upright position; whereas an altered T wave which is normalized by a sympatholytic drug and exaggerated by a sympathomimetic drug or the assumption of the upright position can be related to increased sympathetic tone. Spontaneous fluctuations in the form, amplitude, and polarity of a vagotonic or sympathicotonic precordial lead T wave in successive electrocardiograms on the same subject are likely due to the occurrence of a variation in the

degree of autonomic nervous dysfunction arising from variations in the intensity of the emotional disturbance. The relation of heart rate to the appearance or disappearance of aberrant T waves due to excessive adrenergic or cholinergic impulses cannot be stated with finality at this time.

**Effect of Atropine on Prolongation of P-R Interval**—In a study of the electrocardiograms of seventy-seven patients with active rheumatic fever with P-R intervals of 0.21 second or longer and the tracings of a group of 12 vagotonic persons without a history of rheumatic fever with P-R intervals from 0.22 to 0.34 second, Robinson<sup>8</sup> calls attention to the fact that the administration of 0.0008 gm. ( $\frac{1}{75}$  grain) of atropine sulfate subcutaneously gave rise to a shortening of the P-R interval in each of the two conditions and therefore cannot be used in differential diagnosis. In each case of active rheumatic fever there was shortening of the P-R interval, ranging from 0.02 to as much as 0.18 second. In nineteen cases in which the atropine test was done during the first six weeks of the illness, the average shortening of the P-R interval was 0.052 second; and in fifty-three cases in which the test was done between the second and ninth month of the disease, the average shortening was 0.043 second. The electrocardiograms of the twelve vagotonic persons showed a shortening of the P-R interval in each case, ranging from 0.04 to 0.16 second. These findings present additional evidence that impairment of auriculoventricular conduction in acute rheumatic fever is due, in part at least, to an increase in vagal tone, as suggested by Bruenn (1937).

**Provocative Prolongation of P-R Interval in Rheumatic Fever**—Prolongation of the P-R interval of the electrocardiogram is the most frequent

and most specific electrocardiographic sign of cardiac involvement of acute rheumatic fever, although it is inconstant and frequently transitory. A simple procedure which appears\* to enhance the diagnostic value of prolongation of the P-R interval in acute rheumatic fever has been reported by Gubner, Szucs, and Ungerleider.<sup>9</sup> Prolongation of the P-R interval of considerable degree was produced in twelve of sixteen patients with rheumatic fever by pressure on the carotid sinus, and in many instances the response was augmented by intramuscular administration of 1 cc. of 1:2000 prostigmin twenty minutes beforehand. Prolongation of the P-R interval occurred more commonly in the sitting than in the recumbent position, and more often with left than with right carotid pressure. The effect was more marked when the P-R interval was initially 0.18 to 0.20 second than when it was less than 0.18 second. The changes in conduction were maximal during the acute stages of carditis and tended to disappear as rheumatic activity subsided. Similar pressure on the carotid sinus produced no such effect in sixteen control cases hospitalized for miscellaneous infectious diseases, such as scarlet fever, pneumonia, and upper respiratory infection.

The impairment of atrioventricular conduction in rheumatic fever is believed in many instances to be due to an increased vagal effect, which does not necessarily signify a greater vagal tone as such. The action of the vagus is determined not only by the release of acetyl choline, but also by the rate of destruction of acetyl choline by the tissue enzyme choline esterase. The activity of choline esterase is greatly modified by the pH, its action being maximal in an alkaline medium and falling sharply as the pH shifts toward the acid side. In-

flammatory tissue is characterized by a lowering of  $pH$ , due to accumulation of acid metabolites. Furthermore, the heart is rendered much more sensitive to the action of acetyl choline by anoxemia, which presumably likewise acts by decreasing the  $pH$  in the myocardium. It is suggested therefore that the inflammatory process and vascular changes in the region of the atrioventricular conduction system in rheumatic fever by lowering the  $pH$  and interfering with tissue nutrition inhibit choline esterase, allowing potentiated vagal effect, which is responsible for prolongation of atrioventricular conduction.

**Electrocardiogram and Hypertension**—In a study of 209 consecutive patients, upon whom dorsolumbar sympathectomy was performed at the Massachusetts General Hospital, an analysis by Evans, Mathews, and White<sup>10</sup> of 150 electrocardiograms taken on 132 patients before operation (which were without complicating factors, such as digitalis effect, or congenital or rheumatic heart disease) revealed that 34.7 per cent of the *limb leads* were within the range of normal, 27.3 per cent showed abnormal T waves only (less than 1 mm. in amplitude in lead I), 16 per cent showed left axis deviation only, and 22 per cent showed left axis deviation plus abnormal T waves. Each electrocardiogram was taken in recumbency. The patients' ages varied from twenty-two to fifty-eight years, and the known duration of hypertension ranged from two months to twenty-four years. The diastolic blood pressure on admission varied from 88 to 180 mm. of mercury. Eye grounds and renal biopsies varied from normal to grade 4.

Early electrocardiographic changes consisted of depression of the RS-T junction and segment in lead I, lowering of the T wave in lead I, and lengthening of the

QT interval (Fig. 6). Axis changes occurred simultaneously with T wave changes in lead I but were variable. Sometimes considerable axis change occurred while only slight T wave alterations appeared and *vice versa*. Concomitant with changes in the T wave in lead I, the most frequent change in lead III was an elevation of the RS-T segment. Many times the relative changes in lead III were slight and sometimes the RS-T segment in lead III, as well as that in lead I, was depressed. In the electrocardiograms in which the T waves were normally inverted in lead III, inversion of the T waves first appeared in leads II and III and later in leads I, II, and III when there was considerable change in lead I with only slight change in lead III or when the RS-T segment was depressed in lead III as well as in lead I. Changes in the T wave in lead II almost always occurred in the same direction as those in lead I since changes in lead I almost always predominate over those in lead III, and lead II is the algebraic sum of leads I and III. In the electrocardiograms in which the T waves in lead III were normally inverted, coronary type T waves appeared in the cases in which the last portion of the RS-T segment and the first portion of the T wave became elevated.

The T wave in lead I was inverted in fifty-one instances; this abnormality appeared alone twenty five times, with an inverted T wave in lead II twenty times, and with inverted T waves in leads II and III seven times. An inverted T wave in lead III occurred in fifty-seven cases: Alone thirty six times, with an inverted T wave in lead II fourteen times, and with inverted T waves in both leads I and II seven times. *None of the inverted T waves in lead I alone was associated with abnormal Q waves in lead I.* Two of the electrocardiograms

with inverted T waves in leads I and II had abnormally large Q waves in lead III but not in lead I or lead II; neither of these two patients had angina pectoris. Of the seven electrocardiograms with inverted T waves in leads I, II, and III, none had abnormal Q waves.

the T waves in lead I had become abnormal in 91.7 per cent. Inversion of the T waves in lead II may occur in hearts of "normal" size; it may result from a change in the position of the body. Electrocardiograms tended to become more abnormal as eye-ground changes became

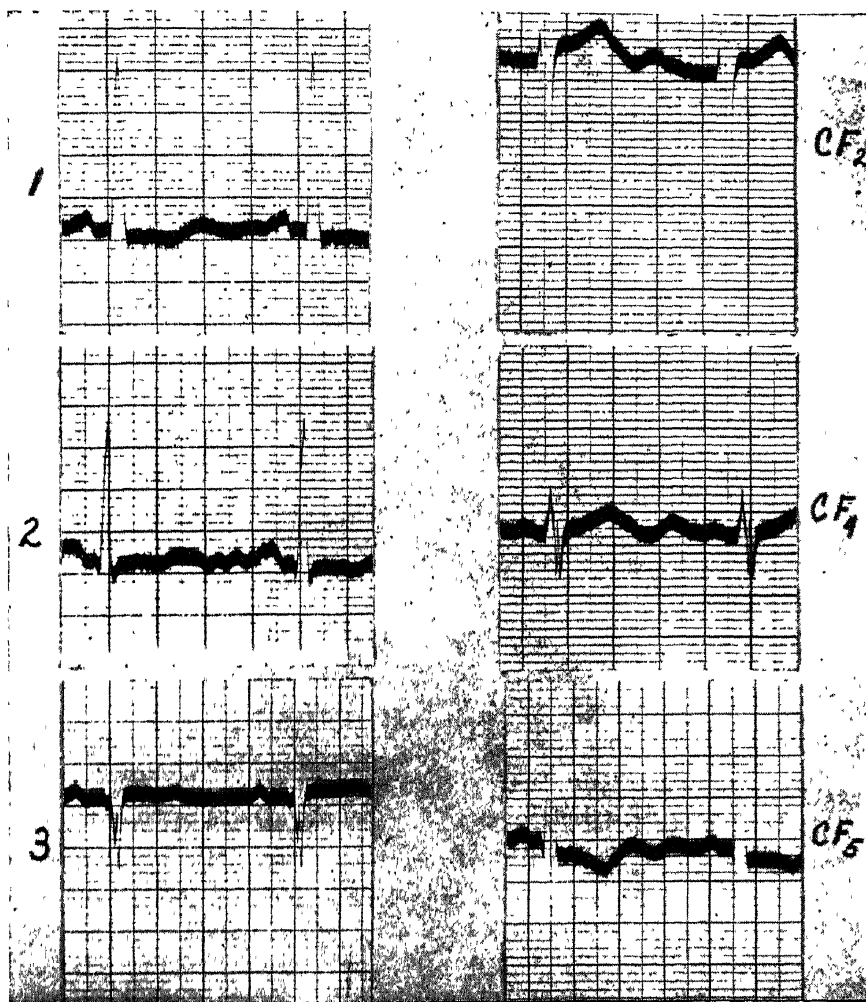


Fig. 6—M. M., a woman, aged 49 years. Electrocardiogram taken Sept. 29, 1943; blood pressure, 270/122. Hypertensive pattern with depression of S-T segments in leads I and CF<sub>5</sub>, slightly inverted T waves in leads I, II, and CF<sub>5</sub>, prominent U waves in leads CF<sub>2</sub> and CF<sub>4</sub>, and inverted U waves in CF<sub>5</sub>.

No definite positive correlation was found between electrocardiographic alterations and the known duration of hypertension, the diastolic blood pressure on admission to the hospital, or the presence of dyspnea. By the time patients complained of pain in the chest, however,

worse. There was no definite positive correlation between changes in the electrocardiogram and those in the renal biopsy material; however, the incidence of abnormal electrocardiograms was distinctly greater in the group with grade 4 renal biopsies than in the other groups.

Abnormal electrocardiogram incidence was only slightly greater in the group with obviously enlarged hearts by roentgen-ray examination than in the one with "normal"-sized hearts. It is quite possible that in some cases the electrocardiogram is a more sensitive index of heart enlargement than is the roentgenogram.

T wave changes in the absence of coronary heart disease are believed to be dependent mainly upon four variables (at least two of which interfere with the normal function of the heart, including conduction): (1) Dilatation; (2) hypertrophy or increased muscle mass without compensatory increase in the vascular bed; (3) increased work with subsequent rise in myocardial metabolism, and (4) rotation of the heart on its longitudinal or transverse axis. Alterations of the T wave in lead II with changes in the position of the body have been reported by various investigators. Abnormalities of the T wave without left axis deviation may be accounted for in several ways: (1) A tendency for T waves to become markedly altered before significant axis changes appear in certain individuals when sudden increase in intraventricular pressure occurs; (2) rotation of the heart in some stocky persons so that the electrical potential of the left ventricle is transmitted to the left leg, and (3) misinterpretation of body build. Some persons who are short and fat and appear to be stocky are fundamentally of thin build as to thorax. Of fifteen patients of thin build, nine (60 per cent) showed T wave changes only, one showed abnormal T waves and left axis deviation, and none showed left axis deviation without abnormal T waves; whereas, of twenty-six patients who were short and fat, or stocky, five (19.2 per cent) had left axis deviation without abnormal T waves, nine (34.6 per cent) had left

axis deviation and abnormal T waves, and five (19.2 per cent) had abnormal T waves without left axis deviation.

An analysis of the electrocardiograms of 100 hypertensive patients in this study revealed definite abnormalities of the T waves of the *precordial leads* in fifty instances. Twenty-five showed abnormal T waves in lead  $CF_5$ , and twenty-five showed abnormal T waves in both leads  $CF_4$  and  $CF_5$ . In thirteen cases T wave changes occurred only in lead  $CF_5$ ; in eleven cases there were changes in both leads  $CF_2$  and  $CF_5$ ; in one case there were rather high T waves in lead  $CF_4$  with a low T wave in  $CF_5$ ; in eleven cases there were inverted T waves in leads  $CF_4$  and  $CF_5$ ; in two cases there were low T waves in lead  $CF_4$  and inverted T waves in lead  $CF_5$ ; in two cases there were inverted T waves in lead  $CF_4$  and low T waves in  $CF_5$ ; in ten cases there were abnormalities of the T waves in lead  $CF_2$  as well as in leads  $CF_4$  and  $CF_5$ . Correlation of the T wave changes in the precordial leads with diastolic blood pressures revealed that the percentage of abnormal leads is greatest in the groups with the highest diastolic pressure. Correlation between heart size and the electrocardiographic changes showed a larger percentage of abnormal tracings in the group with slight or considerable cardiac enlargement than in the group with normal sized hearts. In 39 of the 100 electrocardiograms, both precordial and limb leads showed some abnormality. Abnormal limb leads were accompanied by normal precordial leads in only nine cases, while in eleven cases normal limb leads were accompanied by abnormal precordial leads.

In general, this study has shown that low, diphasic, or inverted T waves in leads  $CF_4$  and  $CF_5$  are commonly found in hypertensive heart disease. These changes are important and helpful, and

may present evidence not found in the limb leads alone. Not infrequently a tracing with a borderline, questionably low T wave in lead I may show abnormalities in the precordial leads which make it consistent with hypertensive heart disease.

tions of hypertensive heart disease in the *limb leads* frequently are reversible by adequate splanchnic resection. The T wave in lead I improved in amplitude (Fig. 7) in 47.1 per cent, became worse in 8.1 per cent, and remained unchanged in 44.8 per cent. Associated with the

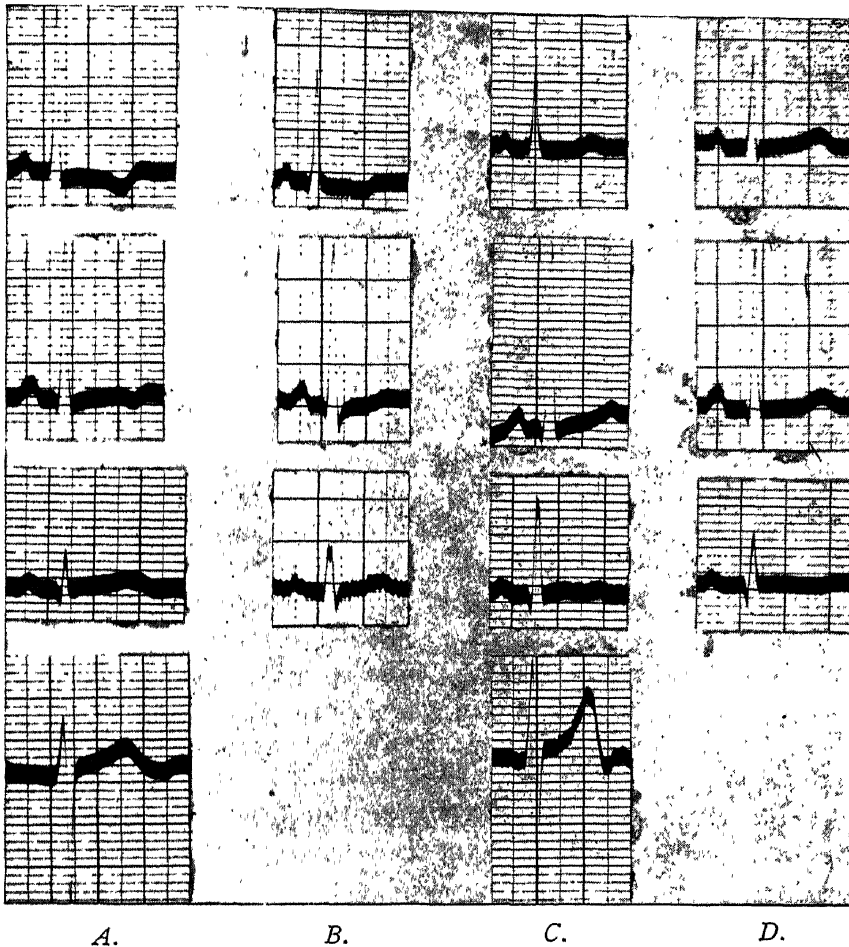


Fig. 7—M. B., a woman, aged 43 years. *A*, Electrocardiogram taken Oct. 15, 1939; blood pressure, 260/110 (lying), 190/110 (standing). *B*, Taken Dec. 26, 1939. *C*, Taken Feb. 9, 1940. *D*, Taken Nov. 25, 1941; blood pressure, 180/110 (lying), 140/100 (standing). Sympathectomy Dec. 21, 1939.

**Effect of Lumbodorsal Sympathectomy on Electrocardiogram**—A comparison by White, Smithwick, Mathews, and Evans<sup>11</sup> of eighty-seven electrocardiograms taken on seventy-four patients after radical lumbodorsal sympathectomy with their preoperative electrocardiograms (which were abnormal) has shown that the electrocardiographic manifesta-

improvement of the T wave in lead I, the most frequent alteration in lead III was a lowering of the T wave. Many times an upright T wave in lead III became inverted, as it should be normally in many individuals. The axis improved in 29.8 per cent, became worse (more to the left) in 12.7 per cent, and remained unchanged in 57.5 per cent.

The electrocardiogram as a whole improved in 57.5 per cent, became worse in 12.7 per cent, and remained unchanged in 29.8 per cent.

As the preoperative eye ground findings and diastolic blood pressure readings on admission became worse, chances for improvement in the electrocardiogram increased. Chances for improvement in the electrocardiogram were not decreased in those with enlarged hearts, in those with a long-standing history of hypertension, or in those in the upper age brackets. The presence of inverted T waves in leads I, I and II, II and III, or I, II, and III preoperatively did not alter the operative or electrocardiographic prognosis unfavorably. The deeper the inversion of the T wave in lead I before operation, the greater was the chance for postoperative improvement in the electrocardiogram. Also the presence of abnormal Q waves in lead III did not alter the prognosis adversely, but it is possible that abnormal Q waves in lead I did so. Improvement in the electrocardiogram was associated with improvement of the diastolic blood pressure. The improvement in the electrocardiogram is more or less permanent; the incidence of improvement or unfavorable change varied little with the length of time following operation.

Comparative studies of the preoperative and early postoperative *precordial* electrocardiograms (leads CF<sub>2</sub>, CF<sub>4</sub>, and CF<sub>5</sub>) of forty-eight patients who underwent lumbodorsal sympathectomy revealed definite improvement in nineteen cases (39.6 per cent). In all cases there was definite improvement in the T waves in both leads CF<sub>4</sub> and CF<sub>5</sub>; and in eight cases there was improvement in the T wave in lead CF<sub>5</sub> alone. There were no significant changes in the QRS complexes or S-T segments.

TABLE VI  
ELECTROCARDIOGRAMS (LIMB LEADS)

	<i>Series of Cases Subjected to Lumbodorsal Sympathectomy</i>	<i>%</i>	<i>Present (Control) Series</i>	<i>%</i>
Improved..	50	57.5	5	10
Same .	26	29.8	20	40
Became worse..	11	12.7	25	50
	87	100.0	50	100

In one of three cases on which follow-up tracings were available a year after operation there was no appreciable change in the precordial leads twenty-three days postoperatively, but there was definite improvement one year later; in the second case there was no significant change either in the records taken twenty-eight days postoperatively or in the one taken one year postoperatively; and in the third case there was a slight progressive change for the worse twelve days and also one year after operation, and a tracing taken three and one-half months afterward was normal. This patient, however, had angina pectoris which was occurring rather frequently, and coronary insufficiency probably accounted for the changes.

A comparison by Canabal, Warneford-Thomson, and White<sup>12</sup> of 240 electrocardiograms of 50 hypertensive patients who were followed for from five to twenty-one years without splanchnic resection with the electrocardiograms of patients who had undergone lumbodorsal splanchnic resection for hypertension revealed that the electrocardiogram in hypertension tends to become worse with the advance of time. There was a striking difference between the spontaneous evolution of the electrocardiogram and the changes which develop after lumbodorsal sympathectomy, much



TABLE VII

DISABILITY RETIREMENT RATE WITH CARDIOVASCULAR RENAL DISEASES, BY AGE, FOR THOSE WITH AND WITHOUT TRANSIENT HYPERTENSION

Age	Person—Years Observed		Retirements with Cardiovascular Renal Diseases		Rate per Thousand		Ratio
	With Transient Hypertension	Without Transient Hypertension	With Transient Hypertension	Without Transient Hypertension	With Transient Hypertension	Without Transient Hypertension	
25-29	2,138	31,103	0	5	0.0	0.2	0.0
30-34	4,424	34,752	3	8	0.7	0.2	3.5
35-39	7,356	35,391	14	18	1.9	0.5	3.8
40-44	10,073	31,819	52	44	5.2	1.4	3.7
45-49	10,964	24,216	98	95	8.9	3.9	2.3
50-54	8,989	14,309	184	148	20.5	10.3	2.0
55-59	6,041	6,981	230	157	38.1	22.5	1.7

in favor of the latter (Table VI). The electrocardiogram of only five of the fifty control cases showed questionable or slight improvement; the tracings of twenty patients (40 per cent) failed to show any appreciable change; and those of twenty-five cases (50 per cent) had an unfavorable evolution. All of the improved cases were women who were less than fifty years of age when the follow-up study began. No favorable changes were observed among the male patients, or in a group of patients older than fifty years. A longer period of time must elapse, however, before final judgment can be passed concerning sustained improvement of the electrocardiogram after lumbodorsal sympathectomy in arterial hypertension.

### Hypertension

**Significance of Transient Hypertension**—An analysis of the medical records of 22,741 officers of the United States Army by Levy, Hillman, Stroud, and White<sup>13</sup> has revealed that the rate for disability retirement with cardiovascular renal diseases was consistently higher

among those with transient arterial hypertension than in those without, at all ages from 35 to 60 years (Table VII). The death rate with cardiovascular renal diseases also was higher in those with transient hypertension, the figures increasing in the older age groups. Both disability retirement and death rates from diseases other than those of cardiovascular renal origin were slightly higher in the group with transient hypertension. The frequency with which transient hypertension was first noted increased with age (Table VIII). The curve of increase was smooth, beginning with 5.9 per cent in the age group of twenty-five to twenty-nine years and reaching a plateau of 18.6 per cent at fifty to fifty-four years of age.

By transient hypertension is meant a reading over 150 mm. of mercury systolic or 90 diastolic which is followed, on any particular examination or at a later examination, by a reading below these levels. The highest systolic and diastolic readings obtained in any one of the series made at a given examination were recorded. By sustained hyper-

TABLE VIII

FIRST OCCURRENCE OF TRANSIENT  
HYPERTENSION, BY AGE

<i>Age</i>	<i>Number Under Observation Throughout Each Age Period</i>	<i>Number Showing First Transient Hyper- tension</i>	<i>Frequency, Per Cent</i>
25-29...	3,020	178	5.9
30-34 .	4,409	396	9.0
35-39 .	5,573	577	10.4
40-44 .	5,150	654	12.7
45-49...	3,478	562	16.2
50-54...	2,101	392	18.6
55-59.	987	183	18.5

tension is meant a reading of over 150 systolic or 90 diastolic persisting throughout an examination and not followed in subsequent examinations by lower levels. A persistent elevation of either systolic or diastolic pressure on a final examination, even though this was its first appearance, was considered to represent sustained hypertension.

Of the total number of 22,741 men, 70 per cent were on active duty when the data were assembled, 17 per cent were retired and still living, and 10 per cent were dead.<sup>14</sup> In only 2 per cent of the total number (448 cases) was the status unknown because the officer had left the Service and could not be traced. Of the 2292 who had died, an autopsy report was available in 639 (28 per cent). The largest number of men, 8252 (36 per cent), were under twenty-five years of age and the numbers decreased progressively in the succeeding five-year periods. Fifty-six per cent were under thirty years of age and 73 per cent were under thirty-five when first examined. Seventy-two per cent were under observation from five to nineteen years, 38 per cent (8671) from fifteen to nineteen years, and in 6 per cent (1437

TABLE IX

LENGTH OF OBSERVATION PERIOD

	<i>Number</i>	<i>Per Cent</i>
Total cases.....	22,741	100
None- single examination	821	3.6
Under 1 year. ....	278	1.2
1 to 2 years .....	1,161	5.1
3 to 4 years .....	2,644	11.6
5 to 9 years.....	3,825	16.8
10 to 14 years....	3,904	17.2
15 to 19 years. . . . .	8,671	38.2
20 to 24 years. . . . .	1,023	4.5
25 years or over....	414	1.8

cases) the observation period was twenty years or more (Table IX). A small number, 821 (4 per cent), were given only a single examination. In most instances, the medical records contained the results of annual physical examinations made between January, 1924, and December, 1941. In many cases record began with admission, as a cadet, to West Point.

All levels of transient hypertension, both systolic and diastolic, were significant with respect to the later development of sustained hypertension and retirement with cardiovascular renal diseases (Table X).<sup>15</sup> Of particular interest was the observation that slight degrees of elevation were important, even when the systolic level alone was involved. Of the greatest significance was a transient rise in diastolic pressure above 100 mm., especially as an early sign of subsequent sustained hypertension (Table XI). No significant differences were apparent between the various degrees of hypertension in relation to the death rates with cardiovascular renal diseases. These data lend support to the view that transient elevations of blood pressure, above the upper range of normal, often represent an early stage of hypertensive vascular disease.

TABLE X

OBSERVED NUMBER OF CASES OF SUSTAINED HYPERTENSION, AND OF RETIREMENT AND DEATH, BY VARIOUS DEGREES OF TRANSIENT HYPERTENSION, COMPARED WITH THAT EXPECTED ON THE BASIS OF THE RATES FOR THE GROUP WITHOUT TRANSIENT HYPERTENSION

<i>Degree of Transient Hyper- tension, Mm. Hg</i>	<i>Later Occurrence of Sustained Hypertension</i>		<i>Cardiovascular Renal</i>			
			<i>Retirements</i>		<i>Deaths</i>	
	<i>Observed</i>	<i>Expected</i>	<i>Observed</i>	<i>Expected</i>	<i>Observed</i>	<i>Expected</i>
150 or less						
91-100	372	129	248	136	75	33
150 or less						
101-150	84	19	62	22	9	5
151-165						
90 or less	32	10	19	12	10	3
151-165						
91-100	122	37	62	43	26	10
151-165						
101-150	111	20	67	24	8	6
166-225						
90 or less	14	3	12	3	2	1
166-225						
91-100	48	16	26	19	2	4
166-225						
101-150	139	26	87	30	20	7
Total.....	922	260	583	289	152	69

The authors conclude that the decision as to the usefulness to the Army of a man with transient hypertension will depend on the need for manpower.<sup>13</sup> During times of peace, or whenever the need for men in the Service is not acute, the transient hypertensive is not to be regarded as a first-rate risk, since later he may prove a burden to the Veterans Administration. It seems probable that the facts pertaining to transient hypertension which have been derived from an analysis of the records of Army officers apply also to the general male pop-

ulation of comparable physical fitness and similar age groups.

**Transient Tachycardia**—A statistical analysis by Levy, White, Stroud, and Hillman<sup>16</sup> of the medical records of 22,741 Army officers revealed that transient tachycardia due to emotional disturbance or some cause not discernible, like transient hypertension of similar origin, is often a precursor of hypertensive vascular disease. By transient tachycardia is meant a heart rate of 100 or over, of sinus origin, which was followed after rest, on any particular examina-

TABLE XI

RATIO OF OBSERVED TO EXPECTED NUMBER OF CASES OF LATER SUSTAINED HYPERTENSION, AND OF RETIREMENT AND DEATH WITH CARDIOVASCULAR RENAL DISEASES, BY VARIOUS LEVELS OF SYSTOLIC AND DIASTOLIC BLOOD PRESSURE

<i>Later Development of Sustained Hypertension</i>				
<i>B. P. Level, Mm. Hg</i>	<i>Diastolic</i>			
	<i>90 or Less</i>	<i>91 100</i>	<i>101 150</i>	
Systolic { 150 or less	(1.0)	2.9	4.4	
{ 151-165..	3.2	3.3	5.5	
{ 166-225..	4.7	3.0	5.3	
Average ratio ..	3.5	3.0	5.1	

<i>Retirements with Cardiovascular Renal Diseases</i>				
<i>B. P. Level, Mm. Hg</i>	<i>Diastolic</i>			
	<i>90 or Less</i>	<i>91 100</i>	<i>101 150</i>	
Systolic { 150 or less	(1.0)	1.8	2.8	
{ 151-165..	1.6	1.4	2.8	
{ 166-225..	4.0	1.4	2.9	
Average ratio ..	2.1	1.7	2.8	

<i>Deaths with Cardiovascular Renal Diseases</i>				
<i>B. P. Level, Mm. Hg</i>	<i>Diastolic</i>			
	<i>90 or Less</i>	<i>91 100</i>	<i>101 150</i>	
Systolic { 150 or less	(1.0)	2.3	1.8	
{ 151-165..	3.3	2.6	1.3	
{ 166-225..	2.0	0.5	2.9	
Average ratio ..	3.0	2.2	2.1	

tion or at a later examination, by a rate under 100. The highest rate obtained during an examination was recorded. Tachycardia was considered to be sustained when a rate of 100 or over persisted, in the recumbent posture, throughout one examination or in a series of reexaminations made in the course of several days.

The frequency of transient tachycardia increased somewhat with age, up to forty-five years; at this point a plateau apparently was reached. The frequency was considerably less than that found for transient hypertension. The group with transient tachycardia showed higher rates for later sustained hypertension and for retirement with cardiovascular renal diseases than did the control group. The rates were similar to those for the group with transient hypertension. In the group with transient tachycardia, the death rate from cardiovascular renal diseases was not significantly greater than in the control group, which finding was in contrast to the group with transient hypertension, in which a significant increase was demonstrated. When both transient tachycardia and transient hypertension were present, the incidence of later sustained hypertension was more than twice as great as when either condition was present alone; the incidence of retirements and deaths with cardiovascular renal diseases was also higher, but to a less pronounced degree.

In a small group with sustained tachycardia, the rates of retirement and death with cardiovascular renal diseases were far in excess of those of any other group considered.

**Transient "O" Diastolic Brachial Pressure**

In the routine examination of men between the ages of eighteen and forty-five years of age for induction into the Armed Forces of the United States, there has been observed by Wilburne<sup>17</sup> in thirty-eight examinees a cardiovascular syndrome characterized by transient "O" diastolic brachial pressure (indirect method), normal or elevated popliteal pressure, and tachycardia. The brachial systolic pressure associated with the "O" diastolic tension ranged from 118 to 250

millimeters of mercury, and averaged 159.1 millimeters. The popliteal systolic and diastolic pressure in the prone position averaged 202.3 and 101.9 millimeters, respectively. The heart rate ranged from 90 to 168 per minute, and averaged 127.4; only two examinees revealed a heart rate below 100. Fifteen of the subjects were between eighteen and twenty years of age, twelve between twenty-one and twenty-five, eight between twenty-six and thirty, two between thirty-one and thirty-five, one between thirty-six and forty, and none between forty-one and forty-five years of age.

Following rest periods varying between five and ninety minutes, the diastolic pressure rose to values ranging from 60 to 112 millimeters of mercury, with an average level of 75.2, while the brachial systolic pressure revealed an average fall of 11 millimeters from the initial (prerest) levels. The popliteal systolic pressure in the prone posture exhibited an average drop of 12.5 millimeters of mercury, and the popliteal diastolic pressure showed an average drop of 7.1 millimeters. The postrest heart rate ranged from 76 to 148, and averaged 104.7, representing a fall of 22.7 beats per minute.

The mechanisms involved in the genesis of this syndrome are difficult to explain. It is believed to represent a marked degree of psychoneurogenic effect on the cardiovascular system. It would be presumed that the nervous tension exhibited by the examinees was an expression of fear, which stimulated adrenal activity; and this resulted in the release of small amounts of epinephrine into the circulation, producing arterial dilatation in the muscle bed of the upper extremities and initiating certain compensatory reflex mechanisms which maintain normal vascular tone or bring about vasoconstriction in the lower extremities, to counteract

the effects of the vasodilatation in the upper extremities in order that physiologic blood pressure levels and adequate cerebral flow be maintained. There also appears to be evidence suggesting that, under certain conditions, the lower extremities may be more responsive to vasoconstrictor influences than the upper extremities. For example, a more pronounced degree of reduction in the skin temperature of the foot than of the hand has been observed as a result of smoking, apparently due to a more marked vasoconstriction in the skin of the lower extremities than in the upper extremities (however, the cutaneous response may not represent the response in the muscle bed).

That these cases do not represent functional aortic insufficiency is evident from the following: (1) An aortic diastolic murmur was absent despite careful repeated search in a quiet room; (2) a brachial diastolic pressure of "0" is generally not encountered in functional aortic insufficiency; (3) no evidence, clinical or roentgenologic, of left ventricular dilatation was found; and (4) the diastolic pressure in the lower extremities did not reveal a corresponding change.

### Subacute Bacterial Endocarditis

**Treatment**—Until a few years ago, subacute bacterial endocarditis was almost uniformly fatal. In a series of 250 cases studied in five Boston hospitals and in private practice from January, 1927, to March, 1939, reported by Kelson and White,<sup>18</sup> no therapy was curative. After the introduction of sulfonamide drugs, cases of unequivocal cures were reported by various investigators. In an analysis by White, Mathews, and Evans,<sup>19</sup> seven (8.9 per cent) of seventy-seven clear-cut and 2 probable cases of subacute bacterial endocarditis, treated with sulfonamides at the Massachusetts General Hos-

pital from January, 1939 to September, 1944, inclusive, recovered; *sulfapyridine* appeared to have a greater antipyretic effect than other sulfonamides. And in a series of cases reported by Kelson,<sup>20</sup> sulfapyridine reduced the fever in a majority, with blood cultures frequently becoming negative for a few days to several months, but only 4 of 197 patients were apparently cured. The failures of sulfapyridine to cure appeared related to complications of the disease, toxic effects of the drug, its bacteriostatic rather than bactericidal mechanism, a low concentration of drug within the vegetations, its ineffectiveness against some strains of nonhemolytic streptococci, and the almost regular development of resistance to its action. The administration of *heparin* in combination with sulfapyridine (or a related drug) was beneficial only when the latter reduced the temperature to normal or near normal and sterilized the blood stream. The incidence of spontaneous cure in subacute bacterial endocarditis has been estimated at 1 per cent.

The use of *penicillin* has opened a new chapter in the therapy of subacute bacterial endocarditis. The early experiences with it were not encouraging; but the use of massive doses has made possible the successful treatment of approximately 75 per cent of cases caused by nonhemolytic streptococci.

By the combined use of *penicillin* and *heparin*, Loewe<sup>21, 22</sup> has obtained a clinical cure in fifty (81 per cent) of sixty-two consecutive and unselected patients (sixty with *Streptococcus viridans* and two with *Streptococcus nonhaemolyticus*). Forty-six of the patients are alive, and many have resumed useful occupations; four have died of other causes. The duration of illness prior to treatment varied from one to six weeks. The penicillin sensitivity of the causa-

tive organisms varied from 0.007 to 0.5 Oxford unit per cc. The average daily dose varied from 40,000 to 2,250,000 Oxford units; and the total individual dosage ranged from 867,000 to 95,620,000 units. Continuous intravenous injection was the choice method of administration. Continuous intramuscular administration was used only in cases of congestive failure or in the presence of severe pyrogenic reaction.

Heparin was administered mostly subcutaneously in the Pitkin menstruum, composed of gelatine, dextrose, glacial acetic acid, and water in definite proportions (which allows a slow and equable absorption). A subcutaneous deposit of 300 mg. of heparin every second or third day (or approximately 200 mg. daily in the form of the aqueous commercial product in the venoclysis) is sufficient to effect an anticoagulant level with a reading of thirty to sixty minutes. A three-day course of penicillin administration intramuscularly before the injection of heparin reduced the incidence of cerebral embolism attending heparinization. In Loewe's experience,<sup>22</sup> it is not feasible technically to give large doses of penicillin—2,000,000 units, daily, intravenously without heparin for without heparin the treatment is often interrupted by the development of thrombophlebitis.

In cases presenting difficulty in obtaining an adequate blood penicillin level because of too rapid excretion of penicillin, para-aminohippuric acid has been administered in doses of 60 to 100 gm. per day in the intravenous drip with penicillin for periods as long as eight days to enhance the blood penicillin level (the excretion of penicillin being delayed by the overloading of the excretory mechanism of the renal tubules by the para-aminohippuric acid).<sup>22</sup>

Fourteen of twenty cases of subacute bacterial endocarditis treated by Dawson and Hunter,<sup>23</sup> with total amounts of penicillin ranging from 830,000 to 36,700,000 units, were in very good health, free from all evidence of infection, at least three months after treatment was ended; one additional patient was in excellent health, free from all evidence of infection, four weeks after the termination of treatment. Heparin was employed as an adjuvant to penicillin in the treatment of the majority.

Five of the cases were selected on a basis of good clinical condition and a well-defined sensitivity to penicillin on the part of the infecting organism, and fifteen cases were unselected, representing consecutive hospital admissions from January to August, 1944. In seven cases the drug was administered by intramuscular injection at frequent intervals, usually every three hours; in five cases an intravenous drip was employed, and in eight cases both methods were used at different times. Therapy was continued for periods varying from ten to sixty-two days. The results were satisfactory in five of the seven cases treated by the intramuscular route and in four of the five cases treated by intravenous drip. For the majority of cases, a regimen of 200,000 units daily for three weeks appeared to be adequate; but in three instances signs of infection recurred when treatment was discontinued, and additional therapy was given. In succeeding courses, the daily dose was increased to 300,000 or 320,000 units and in one case to 500,000 units. Not infrequently the administration of heparin led to sharp febrile reactions, which confused the clinical picture considerably. Hemorrhagic complications resulting from heparinization were observed in only one instance.

Of seven additional cases treated by Dawson and Hunter, in five of which penicillin was administered by continuous intramuscular drip without heparin, the results were as favorable as in the cases in which heparin was employed. In six patients, the infection was apparently terminated, and the seventh patient suffered a relapse after one course of treatment and required additional therapy. Comparative studies showed that, as a rule, higher blood penicillin levels were obtained in patients receiving the drug by continuous intramuscular drip than in those receiving continuous intravenous drip. Since the intramuscular drip is also better tolerated by the patient and the technic is simpler, these clinicians believe that this method of administration is the one of choice when penicillin administration for prolonged periods is necessary.

Of six cases of subacute bacterial endocarditis studied by Paullin and McLoughlin,<sup>24</sup> which were given 200,000 to 300,000 units of penicillin daily by intramuscular injection every two hours, day and night, until about 4,000,000 units were administered, three (aged sixteen, twenty, and sixty-four years) were alive and well six to nine months after discharge from the hospital. The other three cases (aged twenty, sixty-eight, and seventy-two years), in which treatment was unsuccessful, were rather hopeless from the onset.

Of nine consecutive unselected cases of subacute bacterial endocarditis, ranging in age from nineteen to fifty-seven years, treated by Meads, Harris, and Finland,<sup>25</sup> with sodium penicillin at the Boston City Hospital during 1944, seven were alive and free of evidence of active infection for one to eleven months after treatment. The dose generally used was 25,000 units intramuscularly every two hours for approximately two weeks. The

total amount used varied from 3,000,000 to 6,000,000 units except in two cases in each of which a total of more than 9,000,000 units was given in two separate courses. In three cases the blood cultures were negative in four to eight hours and in a fourth case within eighteen hours after the initial dose of penicillin. Two patients had recurrence of infection, one after four months and the other after only one month. It was not certain whether these recurrences represented reactivation of the original infection or reinfection. Heparin was used in three cases, but in two it was discontinued after eight and twelve days respectively, because of a rise in temperature and pulse rate associated with malaise, sweating, anorexia, nausea, drowsiness, and irritability (all of which symptoms completely subsided within twelve hours after the heparin was stopped). All the fatal cases had severe heart failure resulting from extensive damage to cardiac structures.

Intensive penicillin therapy for six to eight weeks resulted in clinical cure, after follow-up periods up to six months, of eight (73 per cent) of eleven patients with subacute bacterial endocarditis caused by strains of streptococcus sensitive in the test tube, studied by Bloomfield, Armstrong, and Kirby.<sup>26</sup> The general plan was to give 200,000 to 300,000 units in twenty-four hours by continuous intravenous drip for three weeks, and thereafter 120,000 to 200,000 units per day in eight intramuscular injections (5000 units per ml. of saline) for three to five weeks. All of the eleven patients were promptly made "bacteria-free" (blood cultures) except one, who died early in the course of treatment. One patient, apparently cured of the infection, died of cardiac failure. Seven patients returned to work and were apparently as well as before endocarditis developed.

There were no clinical relapses or reinfection. Petechiae and emboli continued for some time after the blood cultures were negative. Renal lesions as evidenced by studies of urinary sediment were not as a rule completely eliminated by the treatment. The results of this study indicate that continuous treatment over a long period (two months or more if necessary) is much more likely to terminate the infection completely than brief courses of penicillin, even if the daily dose is large. With the idea of simplifying the technic of administration, the authors are trying a program consisting from the start of intramuscular injections of 50,000 units of penicillin at six-hour intervals.

Of twenty cases with subacute bacterial endocarditis treated by Flippin, Mayock, Murphy, and Wolferth<sup>27</sup> with 300,000 units of penicillin a day for fourteen days as the initial course (administered by continuous intravenous infusion, whenever possible), sixteen had definite subsidence of the infection, twelve are still alive and, with one exception, all are well. Of the eight who did not survive, four were completely free of active infection and died of heart disease, three failed to respond to therapy, and one died of an acute pulmonary embolism soon after treatment was completed. In cases with severe congestive heart failure and in those without suitable veins intermittent intramuscular administration was employed. Patients in moderate cardiac failure tolerated the 3000 cc. of intravenous fluid daily, if the solution was 5 per cent glucose in water and the dietary salt was restricted. Heparin was not used in the treatment of any of the cases.

Ten of the twelve living patients received only a single course of penicillin (4,200,000 units over fourteen days), while the remaining two suffered re-



lapses and required additional treatment. One of the latter (aged twenty-six years) received a total of over 86,000,000 units, administered intermittently over a period of almost twelve months, at the end of which time the blood culture was still positive and the organism (*Streptococcus viridans*) had become quite resistant to penicillin. The organism was then found to be sensitive to 0.05 unit of penicillin X per cc. and following the administration of 15,000,000 units of penicillin X over twenty-five days, the patient has been well for a period of two months. The second patient (aged forty-eight years) suffered three relapses, and then, after receiving 4,200,000 units intramuscularly over a period of twenty-one days, became free from symptoms of the disease for over nine months. Recently, however, she developed signs of early cardiac failure with no evidence of active infection.

In view of subsequent experience with sixteen additional cases, these authors believe that all patients with subacute bacterial endocarditis should receive at least 500,000 units of *penicillin* a day for at least five weeks.

Eleven of twelve patients with subacute bacterial endocarditis treated by Goerner, Geiger, and Blake<sup>28</sup> with massive doses and prolonged courses of penicillin are alive and well; in three cases the time that has elapsed since termination of the treatment has been from one to five months, in four cases from six to ten months, and in another four cases from eleven to fifteen months. The group included one male, aged thirty-five years, and eleven females ranging in age from eleven to sixty-three years. Heparin proved unnecessary in the cure of the eleven successful cases, and its use did not alter the outcome of the single unsuccessful case.

The daily doses of penicillin ranged from 200,000 to 600,000 units for total

periods of from three to nine and one-half weeks in the cases successfully treated. The dose was adjusted (from the basic minimum of 10,000 units per hour) so that the serum penicillin concentration was not less than three times the *in vitro* inhibiting level of the organism concerned in each case. Treatment was chiefly by continuous intravenous infusion day and night except in one case in which the fractional intramuscular route was employed throughout. The daily quantity of the drug was dissolved in not more than 1500 cc. of physiological saline or 5 per cent glucose solution.

When hand or wrist veins were selected as the infusion site, the arm was bound firmly with adhesive tape to a small padded board in such a manner as to splint only the wrist, always leaving the elbow free. When the needle (21 gauge, not longer than one inch) was placed in a forearm (or leg) vein high enough to avoid interference from movement of wrist or ankle, no splint was necessary. The needle was inserted all the way to the shank, with as much of its length as possible lying within the vein. The shank and three-way stopcock were securely fastened with adhesive tape to the skin and also to the splint if one was used. This arrangement usually proved painless and reasonably comfortable, allowing relatively free use of the extremities, and permitted a maximum freedom of movement of the patient in bed or chair (Fig. 8). The three-way stopcock was convenient for taking blood, and for clearing an obstructed needle. The infusion usually was left undisturbed for several days, often as many as five, when a completely fresh assembly was introduced and a new vein on another extremity was cannulated.

In the experience of Goerner, Geiger, and Blake, constant slow intravenous

infusion seemed to be the best method of administration both from the patient's standpoint of maximal comfort and the scientific standpoint of maintaining relatively constant and satisfactory serum penicillin levels with utmost economy. Its successful routine use requires, however, skillful venoclysis technic and relatively close supervision. A course consisting of about 250,000 units daily for four weeks is apparently adequate for

able cases probably would result, although the practice might be wasteful of penicillin, and the occasional case with an unusually resistant organism probably would not be cured because of inadequate dosage.

The administration of relatively small doses of penicillin before obtaining a positive blood culture in suspected cases of subacute bacterial endocarditis should be avoided because (1) the chances of



Fig. 8.

the treatment of the majority of the relatively early cases in which physical deterioration is not notably advanced, and the infecting organism is satisfactorily inhibitable.

When facilities for estimation of the resistance of the infecting organism to penicillin *in vitro* and measurement of the serum penicillin titers during treatment to ensure effective therapy are not available, the simplest therapeutic practice would be the injection of penicillin intramuscularly in doses of at least 30,000 units at intervals of not longer than two hours day and night for at least four weeks. Cure of many of the favor-

obtaining a positive blood culture are lessened, despite the addition of penicillinase to the culture material, (2) the infecting organism may lose its sensitivity to penicillin, and (3) the cardiac lesion itself undoubtedly progresses.<sup>27</sup> In cases in which routine blood cultures are negative, positive results may be obtained at times by employing anaerobic and arterial cultures.

From the results of the studies made by various groups of clinicians mentioned in this discussion, it appears that the use of anticoagulant agents as therapeutic supplements to penicillin is not essential in the successful treatment of subacute

bacterial endocarditis. As stated by Goerner, Geiger, and Blake,<sup>28</sup> "it is conceivable that if the surfaces of vegetations can be kept sterilized for several weeks, epithelialization of the surface and fibrotic scarring of the thrombotic mass may effectively incarcerate and perhaps ultimately destroy bacteria lying beneath." That anticoagulant medication may be unnecessary has also been suggested by Lichtman's survey (1943) which showed that the cure rate of 109 cases of bacterial endocarditis treated with *heparin* and *sulfonamides* was only 2.5 per cent higher than obtained in 489 cases treated with sulfonamide compounds alone. Heparin is potentially a dangerous drug, especially in a disease in which embolic phenomena are common. The maintenance of continuous heparin effect for weeks considerably complicates the technical management; the drug often causes fever which confuses the clinical course; and its administration calls for at least daily estimation of the coagulation time to ensure proper control of the dosage. Finally, heparin is expensive; the required daily amount costs more than the penicillin and adds hundreds of dollars to the cost of treatment of the average case. Whether heparin will prove advantageous in the treatment of far advanced cases with perhaps more massive vegetations is yet to be learned.

*Accessory Therapeutic Measures*—Accessory therapeutic measures in the treatment of subacute bacterial endocarditis include the use of high caloric, high vitamin diets, supplementary multivitamin preparations, hematinics in liberal dosage when anemia is present, and frequent transfusions when indicated. The administration of digitalis and the restriction of the salt and fluid intake may be necessary in patients presenting signs of myocardial insufficiency.

*Foci of infection* in abscessed teeth, diseased tonsils, and so forth should be eliminated. But a course of treatment with penicillin or sulfonamides or both should be given before and after tonsillectomy or tooth extractions as a prophylactic measure. A regimen for adults, suggested by Anderson and Keefer,<sup>29</sup> is the administration of 2 gm. of *sulfadiazine* twenty-four hours before operation, and 1 gm. every four hours for forty-eight hours after operation; or 50,000 or 100,000 units of penicillin can be given intramuscularly no longer than one-half hour before the projected operation, and 25,000 units intramuscularly every three hours for twenty-four to forty-eight hours after operation. A similar course of therapy should be of advantage immediately after any embolic manifestation in spite of the finding of negative blood cultures. The eradication of foci of infection may be done as early in the span of treatment as is consistent with the condition of the patient.

*Criteria for Cure*—A favorable response to treatment in subacute bacterial endocarditis is marked by a fall in temperature to normal, a sense of well-being on the part of the patient, improvement of appetite, disappearance of embolic phenomena, splenomegaly and clubbing of fingers, progressive gain in weight, improvement in the hematologic picture, and decrease in the sedimentation rate. For the first three months after treatment with penicillin, the prognosis should remain extremely guarded. If the patient remains well during this period, the prognosis improves, but—because of the possibility of merely a temporary therapeutic remission—it is unwise to consider any patient as cured until at least a year has elapsed after the termination of treatment. Embolic phenomena may occur for some time after the blood becomes bacteria-free;

and each such occurrence carries with it the threat of further damage to valves or other underlying structures in the heart from which the emboli are released, as well as possible injury where lodgment occurs. Severe cardiac failure may follow these incidents. The likelihood of reinfection will probably always be present in these patients with acquired or congenital endocardial defects. In most instances, several weeks or, more often, several months, of convalescence are required before the patient has recovered fully his strength and energy. Restriction of physical activities during the period of convalescence is of importance.

### Acute Bacterial Endocarditis

The diagnosis of acute bacterial endocarditis is difficult to make with certainty during life. The disease manifests itself in two distinct forms, *viz.*, cases in which infection of the endocardium is primary, and cases in which it is secondary. In the primary form, the patient presents the symptoms and signs of a constitutional infection without any evidence of localization; the blood culture usually is positive; but the pathognomonic signs, such as the appearance of new or changing heart murmurs and the development of petechiae or other embolic phenomena, may be absent until late in the disease, and occasionally never develop. Much more frequent is the secondary form of the disease, in which bacteria gain access to the blood stream from a frank focus of infection. The diagnosis may be difficult, however, because pathognomonic signs may not be present and attention usually is fixed on the primary focus of infection. It is not unusual for the diagnosis of bacterial endocarditis to be suspected only when progressive improvement in the primary focus impels search elsewhere for the cause of the continuing symptoms and bacteremia.

Before the introduction of *penicillin*, it is doubtful whether any patient with acute bacterial endocarditis, other than a few cases caused by the gonococcus, ever recovered. During the two years just passed there have been reports of cases that have recovered under treatment with penicillin. According to Anderson,<sup>30</sup> the recovery rate is approximately 45 per cent in cases caused by the hemolytic streptococcus, 35 per cent in cases caused by the pneumococcus, and 25 per cent in those caused by the staphylococcus. The optimum schedule of treatment is not yet known. This is partly due to the fact that the patient either recovers or succumbs to the infection within a few days, and there is little opportunity to experiment with dosage.

In patients who have developed valvular defects, the appearance of severe cardiac failure after the infection has been controlled has frequently constituted a serious obstacle to complete clinical recovery. In some instances, death has occurred within a few weeks or months from cardiac failure; others have remained seriously incapacitated.

Of seven cases of acute bacterial endocarditis treated with penicillin by Meads, Harris, and Finland,<sup>25</sup> three (one caused by type 7 pneumococcus, one by type 5 pneumococcus, and the third by group A, type 28, hemolytic streptococcus) survived. Small doses were generally used in these cases because of the greater susceptibility of the infecting organism. The diagnosis in all the fatal cases was confirmed at autopsy but in those which survived, it is only highly probable. Heparin was used as an adjuvant to penicillin in two cases, one of which recovered.

In a series of six cases of acute bacterial endocarditis (three due to hemolytic streptococcus group B, two to *Staphylococcus aureus*, and one to hemolytic

streptococcus group A) treated with moderate doses of penicillin by Dolphin and Cruickshank<sup>31</sup> in the puerperal sepsis unit at the North-Western Hospital, three were alive and well six to twelve months after penicillin therapy was stopped. The total dosage of penicillin in the three cases which recovered was 790,000, 960,000, and 2,300,000 units, respectively; and in the three fatal cases, 646,000, 960,000, and 1,157,000 units, respectively. Attention is called to the frequency of infection of healthy heart valves by group B streptococcus, which not uncommonly causes mild genital tract sepsis, particularly after abortion.

### Peripheral Vascular Disease

**Psychiatric Factors in Peripheral Vasoneuropathy After Chilling**—In a study of twenty-four cases of peripheral vasoneuropathy after exposure to severe cold ("trench foot"), Osborne and Cowen<sup>32</sup> have observed a common incidence of a history of sweaty hands and feet and a tendency to neurosis. In one group of fifteen infantrymen without previous battle experience, subjected to ice and snow, morale was low, the incidence of neurotic traits high, and all gave a history of previous hyperhidrosis, usually affecting the hands and feet; ten patients admitted almost uncontrollable fear while in action, at various times before the development of trench feet. In the second group of nine men from an armored formation, most of them battle trained and with high morale, there was a low incidence of psychoneurotic or psychosomatic illness, although five were of the "perspiratory personality" type. With due allowance for the fact that the degree of exposure in the two groups of cases was not strictly comparable, the severity of tissue damage was greater in the first group.

The clinical findings in this study suggest that the individual prone to psychoneurosis, of poor morale, develops a more severe peripheral vasoneuropathy than the man of sound personality and good morale, under equal conditions of exposure to severe cold and with the same lack of opportunity for adequate foot hygiene. The neurotic individual has a parallel unstable vasomotor system, and the hypersensitive neuromuscular control may make the arterioles more susceptible to trauma from cold. Furthermore, the temperature-regulating mechanism of the skin in this type of person is unstable and hypersensitive; and, as a rule, the sweat glands are overactive, though perspiring freely, the skin is cold, and he feels cold—the "cold perspiration" of anxiety. Such skin, already "cold and clammy," must be at a disadvantage when exposed to external chill and dampness. The prophylaxis of trench foot thus becomes as much a matter of personnel selection as of "foot hygiene"; and in its treatment the psychiatrist sometimes will be able to accelerate both recovery of function and return to some form of useful duty.

**Neurovascular Syndrome Caused by Hyperabduction of Arms**—A neurovascular syndrome produced by prolonged hyperabduction of the arms, which may give rise to gangrene secondary to occlusion of the subclavian artery and neurologic sensory complaints probably secondary to stretching and ischemia of the brachial plexus trunks, has been described by Wright.<sup>33</sup> By "hyperabduction" is meant that phase of circumduction which brings the arms together above the head (with the elbows flexed or with their long axes corresponding in plane to that of the body). Of five cases reported by Wright, four developed their syndromes as a result of prolonged sleeping in the supine position

with their arms hyperabducted, and in the fifth case the symptoms were aggravated by two injuries involving the right shoulder. In additional cases, to be reported later, the syndrome has developed as the result of occupational hyperabduction.

stances, obliteration of the pulse could be produced by merely hyperabducting the arm, and sometimes occurred before the arm reached  $180^{\circ}$ ; in others, it was necessary to apply moderate stress to the arm, forcing it posteriorly and moving it about in order to find a position in



Fig. 9—Sleeping position frequently seen in hospital wards, in which obliteration of the pulse and overstretching of the nerve trunks may occur.

A study of 150 young adults, considered to be normal with regard to this syndrome, revealed that occlusion of the subclavian artery by hyperabduction of the arms is a normal phenomenon. In 125 (83.3 per cent) of the 150 "normal" subjects, obliteration of the right arm pulse could be produced by hyperabduction of the right arm above the head (Fig. 9); and in 124 (82.7 per cent), obliteration of the left arm pulse could be produced by hyperabduction of the left arm above the head. In some in-

stances, the pulse was obliterated. No correlation was found to exist between the degree of muscular development and the ease with which the pulse could be obliterated. Turning the head toward, or away from, the arm being tested may open or close the subclavian-axillary artery; in this group the scalenus muscles may play an important part. Flexing the head and neck reduces the incidence of obliteration, and hyperextending increases the incidence. The frequency of obliteration of the pulse in this "normal"

group is of importance because this position of hyperabduction is being widely, but erroneously, used as a test for the scalenus anticus syndrome. Actually, the scaleni are relaxed rather than tensed in this position.

between the clavicle and the first rib (Fig. 10). The subcoracoid - pectoralis minor syndrome appeared to play a major role in the obliteration of the pulse caused by hyperabduction, for it occurred when the arm was abducted

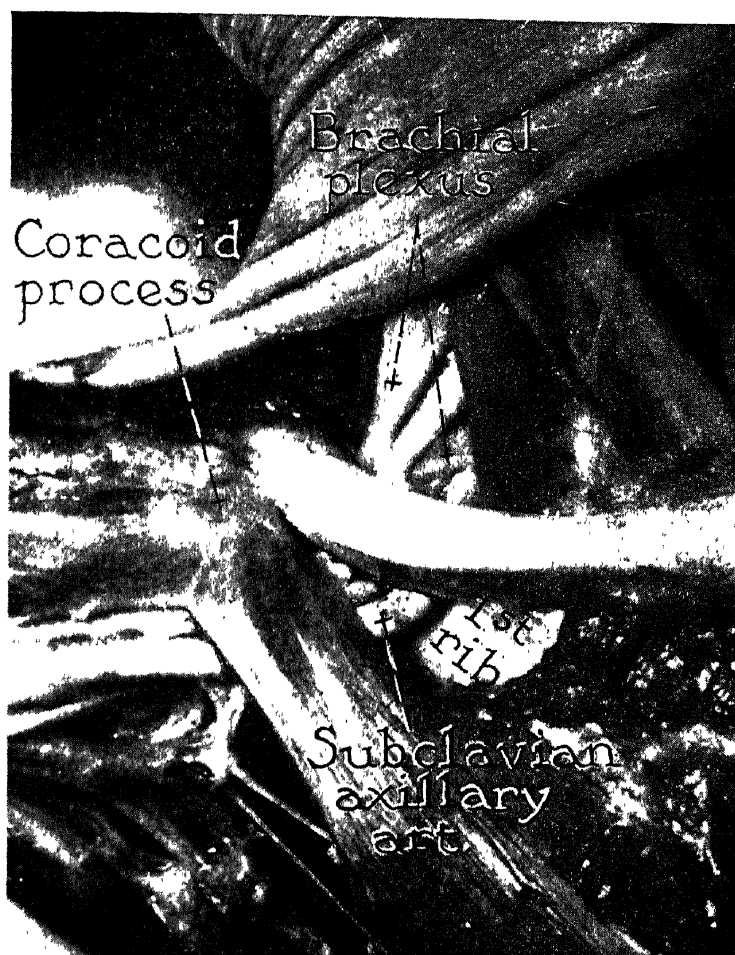


Fig. 10—Photograph showing relations of brachial plexus and subclavian-axillary artery with the arm in hyperabduction. In many instances in this position the vessels and nerves are stretched and subject to torsion as they pass beneath the coracoid process and behind the pectoralis minor muscle. Marked torsion and pinching may also take place between the clavicle and the first rib.

In the production of this syndrome, there are two zones of stretching, torsion, and pinching: (a) The point at which the axillary-subclavian vessels and the trunks of the brachial plexus pass posterior to the pectoralis minor muscle, just beneath the coracoid process; and (b) the point at which the subclavian vessels and the trunks of the plexus pass

anterolaterally to 90°, a position in which the costoclavicular space is at a wide phase. Reduction in the width of space between the clavicle and the first rib may have played a major part in the instances in which obliteration of the pulse occurred only with difficulty, and with backward pressure, as well as hyperabduction. Pathologic changes are rela-

tively uncommon because (1) only a small number of people sleep or work with their arms hyperabducted for long periods of time (as in painting a ceiling); (2) most of these individuals will change their position by bringing their arms down below shoulder level when discomfort develops; and (3) in many instances the arteries are obstructed or the nerves stretched excessively only in certain specific positions.

The findings in this study emphasize the importance of directing special attention to the state of the pulse and complaints of paresthesias and numbness from patients whose arms are in hyperabduction on operating tables or in splints or casts. Persons whose pulses can be occluded in the hyperabducted position should refrain from sleeping or working with their arms in this position.

### Treatment of Edema

**Fluid Dynamics in Chronic Congestive Heart Failure**—Various theories have been presented to explain the alteration in the fluid dynamics of congestive heart failure. According to the rather general present teaching, edema occurs primarily as a result of an increase in venous pressure which arises from the damming up of blood in the venous system when the ability of the heart to propel blood forward is impaired, and increased capillary permeability and decreased colloid osmotic pressure of the blood act as contributing factors. But in the opinion of Warren and Stead,<sup>34</sup> the development of edema in chronic congestive heart failure is due primarily to failure of the kidneys to excrete salt and water normally, which in turn gives rise to an increase in the quantity of extracellular fluid; and the increase of extracellular fluid is followed by an increase in plasma volume and a subsequent increased production of plasma

protein, which in due time cause a rise in venous pressure. The impairment of renal function is believed to be related directly to the decreased cardiac output and not to engorgement of the kidneys from an increased venous pressure, because the salt and water retention may occur before there is a rise in venous pressure and may persist for a considerable time after the venous pressure has returned to normal.

Patients with hypertension, aortic insufficiency, and coronary arteriosclerosis usually begin to have dyspnea before an elevation of venous pressure occurs, and many of them become orthopneic, with a normal systemic venous pressure. That an abnormally large volume of extracellular fluid is present in these patients, in spite of but little demonstrable edema, is shown by a rapid loss of 2 to 10 kg. of weight when placed in bed and treated for congestive failure. Patients with repeated attacks of paroxysmal nocturnal dyspnea but without obvious edema often show striking improvement when the urinary output is increased by the administration of a mercurial diuretic (Alsever and Levine, 1938). Gain in weight due to increase in extracellular fluid and increase in plasma volume (as shown directly by the dye technic and indirectly by a fall in the hematocrit reading) have been observed to precede a rise in venous pressure in patients with myocardial disease under observation in the hospital when congestive failure has been precipitated by the administration of large amounts of sodium chloride.

Much of the difficulty in studying the development of edema is due to lack of knowledge of the mechanisms controlling the amount of extracellular fluid normally present in the body. In congestive failure the cardiac output is inadequate to meet the demands of the patient's daily life, and, as a result, the kidneys are



no longer able to excrete salt in a normal manner, and the retention of salt leads to the secondary retention of water. Various investigators — Schroeder (1941), Proger, Ginsberg, and Magendantz (1942), and Schenmm (1942, 1944)— have shown that with an extremely low intake of sodium chloride, water is not retained by the patient with myocardial insufficiency. In such cases, even the amount of sodium chloride in the average diet is sufficient to give rise to considerable retention of water. The importance of the sodium ion in the retention of salt and water is indicated by the fact that salts such as potassium chloride and ammonium chloride fail to cause retention of water and are even diuretic, and that sodium bicarbonate acts in almost the same way as sodium chloride in causing retention of water. As far as can be determined, increasing and decreasing the sodium chloride intake of patients with congestive failure induce and relieve the manifestations of congestive failure without any corresponding change in cardiac output. Increased capillary permeability apparently is not a primary factor in the development of edema in heart failure, for repeated investigations have shown that the protein content of the edema fluid is low, usually less than 0.5 gm. per 100 cc.

For years it has been known that the blood volume in congestive heart failure is increased. The increase is primarily in the plasma volume, although the red cell volume also may be increased. As shown by various investigators, the plasma volume and the extracellular fluid volume increase and decrease concordantly. When hemodilution occurs because of the retention of salt and water, the lowering of the concentration of the plasma proteins serves as a stimulus for the production of more plasma protein and as a consequence the

total quantity of circulating protein also usually increases. The plasma volume is thus increased without a marked lowering of the osmotic pressure of the plasma proteins. When the fluid content of the body is decreased by therapy and the plasma volume returns to normal, the quantity of circulating protein also returns to normal (Seymour, Pritchard, Longley, and Hayman, 1942). It is probable that the pressure rather than the volume of the extracellular fluid is important in determining the plasma volume. When the plasma protein concentration is low, a much greater increase in the quantity and pressure of the extracellular fluid is required to maintain a sufficiently large plasma volume to produce a high venous pressure. In a study of the venous pressure immediately after death in patients with and without congestive heart failure, Starr (1940) found that in patients with prolonged congestive heart failure the venous pressure remained elevated after death, and concluded that the greater part of the rise in pressure was related to the increase in blood volume rather than to an actual change in the dynamics of a failing circulation, such as an increase in tone of the vascular bed or the damming up of blood behind a failing right ventricle.

Although a generalized increase in venous pressure is not the primary cause of edema in congestive heart failure, local increases in venous pressure are of great importance in the placement of fluid which is retained in the body because of the failure of the kidneys to excrete salt and water in a normal manner. In the ambulatory patient, visible edema appears first about the ankles, where the venous pressure is greatest (being the sum of that in the great veins of the chest and that produced by gravity). In patients who have not lost weight, the quantity of extracellular fluid neces-

sary to support a high plasma volume and a high venous pressure may be detected clinically only with difficulty. In the patient with tight skin, such as frequently found in Negroes, less retention of water is necessary to build up tissue pressure, and therefore such an individual maintains a high venous pressure with less edema than does one with loose, flabby skin. And in the patient with salt and water retention, who is subject to episodes of increased pulmonary capillary pressure due to momentary discrepancy in the output of the right and left ventricles, marked pulmonary edema may occur with relatively little edema elsewhere.

In sudden acute heart failure, increase in venous pressure may result from an increase in venous tone secondary to the marked decrease in cardiac output and from a redistribution of blood in the vascular bed. This may be caused reflexly by the fall in cardiac output or by a humoral mechanism from the decreased renal blood flow. Strengthening of the heart by digitalis may cause an increase in the cardiac output and a rapid decrease in venous pressure. In many patients the rise in venous pressure represents a summation of the effects of a large plasma volume and of a redistribution of blood secondary to an episode of more acute heart failure.

**High Fluid Intake in Management of Edema**—Only in the fifty years just passed has the limitation of fluids in the presence of edema been the almost universal practice. Earlier clinicians noted that the theoretical fear of water in dropsy was not justified by close bedside observation. In 1777, William Withering said: "I allow, and indeed enjoin, my patients to drink very plentifully of small liquors through the whole course of the cure." Austin Flint (1886) and Sir William Osler (1896) believed that in

nephritis "of all diuretics, water is the best." And Newburgh (1934) observed that edema in nephritis yields to an intake of water as high as 4 liters daily.<sup>35</sup>

In an eight-year study of 402 cases with either marked gross edema or advanced cardiovascular disease (in 626 separate periods of treatment) it has been found by Schenm<sup>35</sup> that large amounts of water are tolerated without ill effect, particularly by patients with gross cardiopathy. The results were better than those obtained with restriction of fluids, whether the primary illness was heart disease, nephritis, eclampsia, pernicious anemia, or some "idiopathic" syndrome. The presence of findings such as increased venous pressure, low concentration of plasma proteins, acute pulmonary edema, convulsions, choked optic discs, low fixed specific gravity of the urine, or marked chloride or sodium deficits did not prove a contraindication to the regimen.

In 393 periods of observation on 241 cases with gross edema (Table XII), the edema cleared entirely in 369 instances (94 per cent) with a high fluid intake. Most of the twenty-four instances (6 per cent) in which the regimen failed were cases of advanced disease with the uremic syndrome, in which the oral intake was negligible because of nausea, vomiting or semistupor. In 103 (26 per cent) of the 393 periods of treatment, no change except the institution of the high fluid intake regimen was made, and therefore the benefit could not be attributed to factors such as rest, or the administration of digitalis, oxygen, or diuretic drugs. Oppressive degrees of hydrothorax or ascites rarely required aspiration. In thirty-nine cases (fourteen with chronic valvular disease and twenty-five with degenerative heart disease) which had been disabled by anasarca for from one

TABLE XII  
GROUPS OF THE 241 CASES WITH GROSS EDEMA

Simple hypertensive and arteriosclerotic heart disease	70	<i>Main Groups</i>			
Acute myocardial infarction	40				
Resistant ascites, with cardiopathy	13				
Advanced general vascular disease	11				
Diabetes mellitus with anasarca	10				
Cor pulmonale (7), Thyrogenic ht. dis. (3)	10				
Heart Disease, Degenerative, Progressive	Totals	154	84	70	60.9 yrs.
Mitral stenosis and/or aortic insufficiency	38				
Same, with acute rheumatic pancarditis	6				
Same, with viridans endocarditis	4				
Heart Disease, Rheumatic, Chronic Valvular	Totals	48	14	34	41.6 yrs.
Nephrosis	10				
Acute and subacute nephritis	13				
Eclampsia (5), lymphoblastoma (5), pernicious anemia (3), other cases (3)	16				
Renal Disease and Other Cases	Totals	39	19	20	34.0 yrs.
Gross Edema Cases	Totals	241	117	124	52.5 yrs.

to nine years in spite of treatment by the usual methods, the edema disappeared on the high fluid regimen and was so well controlled that they resumed nearly normal activity and were economically useful again for periods of from one to eight years.

Marked edema disappeared with the high fluid intake regimen also (a) in cases of myxedema with basal metabolic rates below minus 30 before the administration of thyroid extract; (b) in cases with deficient diets from habit or chronic illness before a diet adequate in protein or vitamin B was given, and (c) in pernicious anemia even, when complicated by spinal cord changes, before the blood or general condition improved. In acute febrile illnesses in which edema and oliguria had developed from the diversion of water to edema formation by sodium retained from excess basic ash on the customary liquid diets of salted soups,

fruit juices, and milk, the disorder was corrected by a change to neutral or acid-ash liquids. Edema or oliguria also was relieved by substituting *calcium carbonate* for sodium bicarbonate in peptic ulcer cases, *acetylsalicylic acid* for sodium salicylate in severe rheumatic fever, and *vitamin concentrates* for large amounts of orange and tomato juice in surgical cases. Some cases with mild cardiac disease but marked edema who had been on diets high in basic ash or salted foods cleared 15 or 20 pounds of edema without the use of digitalis or acid drugs. In very ill nonedematous patients, the regimen with its regulation of sodium proved useful in the correction of dehydration and anuria.

The fundamental principle on which the high fluid intake and restricted sodium regimen are based is that salt retention is the primary factor in the formation of edema, and that the alkaline

edema fluid is retained in the body unless the bicarbonate fraction of its sodium salts is used up by the metabolic acids or by ingested acids. Acidification incites the kidneys to balance the threat to the hydrogen ion concentration of the body fluids by the elimination of neutral or acid sodium salts or, as often expressed, "acidification mobilizes the sodium." The sodium is excreted by the kidneys in the urine; water reaches the kidneys only after all other demands of the body for water are met; and the amount of urine water needed for the elimination of the sodium depends upon the functional capacity of the kidneys. Sufficient water therefore must be supplied to the body so that enough water will reach the kidneys for the elimination of the sodium. The aim of the regimen is (1) to decrease the ingestion of sodium and to encourage the mobilization of sodium already retained, by giving a diet restricted in sodium and yielding a neutral or acid ash; (2) to increase and hasten the normal effect of the metabolic acids, by the administration of minimal amounts of acid drugs, and (3) to facilitate elimination of the mobilized sodium by the kidneys and avoid the development of true cellular dehydration by administering plain water in adequate amounts.

The diet is not simply a low salt diet; at all times it must yield a neutral or slightly acid ash. Its construction depends simply on the knowledge that milk, all vegetables, and all fruits (except prunes, plums, and cranberries) yield an excess of alkaline ash. Therefore, not only must table salt and sodium salts be restricted but at each feeding the foods just mentioned must be balanced with foods that yield an excess of acid ash, which are meat, chicken, fish, eggs, cereal foods (including corn), and the three

excepted fruits mentioned above. (See *Initial Neutral Diet*.) The Karel diet at the point when eggs, cereal, and toast are added, if low in salt, is such a diet. Patients must be warned against commercial salt substitutes (mainly sodium salts of some acid), "soda" and commercial alkalis for indigestion, and forcing fluids with unlimited amounts of milk or alkaline fruit juices. Extra alkaline fruit juice or milk can be fairly well balanced by about 15 drops of dilute hydrochloric acid to the cup.

Edema usually disappeared slowly, but often with surprising rapidity, with simply the neutral diet and an abundance of water, sufficient acid being supplied by the physiologic process of metabolism to use up the bicarbonate fraction of the stored sodium mixture and incite its elimination. Practically, however, for psychological and economic reasons as well as for comfort, acid drugs were often used to speed the elimination of edema. When the oral intake was well established or the initial neutral diet was tolerated, 5 to 10 drops of *dilute hydrochloric acid* were given in a full glass of water every hour from 7:00 A. M. to 7:00 P. M. (or 15 to 30 drops at each feeding). If the acid was not tolerated, *ammonium chloride* was prescribed in doses of 2 or 3 gm. a day (rarely in an amount greater than 15 grains four times daily). After dismissal from the hospital, only the more severe cases, or milder cases which neglected the diet grossly, needed the acid medication.

In mild cases of edema, a total of 2500 to 3000 cc. of water daily is given trial as a minimum, leaving the water derived from the nonliquid portion of the diet (700 to 1200 cc.) as a safe margin. A severely dehydrated, edematous patient with severely impaired kidneys and with a fever or much sweating

TABLE XIII  
INITIAL NEUTRAL DIET  
*Six Small Feedings, with Protein 60-70, Calories 2400*

<i>Food</i>	<i>Wt.</i>	<i>Measure</i>	<i>Food</i>	<i>Wt.</i>	<i>Measure</i>
	<i>gm.</i>			<i>gm.</i>	
1. <i>Cereal and Cream</i>			2. <i>Eggnog</i>		
Cereal prepared	15	$\frac{3}{4}$ cup	One egg	—	—
or uncooked	15	1 tbsp.	Milk	100	$\frac{1}{2}$ cup
or cooked	100	$\frac{1}{2}$ cup	Cream 20%	100	$\frac{1}{2}$ cup
Cream 20%	100	$\frac{1}{2}$ cup	Sugar and spice	—	—
Sugar	10	2 tbsp.			
3. <i>Fruit, Bread and Milk</i>			4. <i>Corn Soup</i>		
Prunes	100	$\frac{1}{2}$ cup	Corn purée	70	$\frac{1}{3}$ cup
Bread	30	1 slice	Bread	30	1 slice
Butter	10	1 pat	Butter	10	1 pat
Milk	200	1 cup	Cream	70	$\frac{1}{3}$ cup
5. <i>Eggs, Toast and Milk</i>			6. <i>Bread and Milk</i>		
One egg	—	—	Milk	200	1 cup
Bread	30	1 slice	Cream 20%	30	1 tbsp.
Butter	10	1 pat	Bread	60	2 slices
Milk	200	1 cup	Butter	15	1 tbsp.
Cream	30	2 tbsp.			

Notes: Whole wheat bread prepared without salt; butter to be unsalted or washed.

Cereal prepared without salt; farina, cornmeal, cracked or ground whole wheat, oatmeal, puffed rice or puffed wheat only.

Any one feeding may be repeated or substituted for another, but the two eggs and the milk for the day must be taken. Extra bread, cereal and eggs may be taken if patient is not overweight.

*When digestion is weakest* prunes should be souffled and the corn soup feeding replaced by feeding 6.

*When digestion is stronger* plums and cranberries may be used in addition to prunes; and chicken, fresh fish or lamb substituted for the egg in 5.

*Additional Liquids:* Weak tea or coffee with sugar; unsalted weak chicken or beef broth.

Prunes, plum and cranberry juices well diluted in water (1:4). Water flavored with fruit flavoring (Kool-Aid, etc.).

*Desserts:* Clear jello, wine jelly, angel food or sunshine cakes; as desired.

#### *Precautions for Home Use*

1. No food or drink other than above. All of each feeding must be eaten.
2. No salt substitutes except the Ammonium Chloride furnished you.
3. No soda or alkali medicines for "gas" or indigestion other than the Calcium Carbonate furnished you.
4. Measure out three quarts of water and take by 7:00 P.M.
5. Take two to five drops of the liquid medicine furnished you in a glass of water every hour until 7:00 P.M.

might require 8,000 to 10,000 cc. of water for a day or two, and 4000 to 5000 cc. daily thereafter. When nausea or vomiting or stupor is present, or for other reasons an adequate amount of water cannot be given orally, enough intravenous solution is given to bring the total intake up to the estimated desirable amount. *Isotonic dextrose*, 5 per cent in distilled water, yields a maximum of plain water for the use of the body. Normal saline solution is not given parenterally unless marked clinical signs of hypochloremia are presented, or the carbon dioxide combining power is very low. So-called "water intoxication" was not encountered although syndromes were seen which were found to be due to loss of body fluid *volume* or disturbance of electrolyte pattern, or to "true" dehydration. The correction of these extracellular fluid defects was effected by giving a *proper* amount of salt and a generous excess of plain water, particularly when renal function was badly impaired—indicating that almost up to the point of cessation of cell function the kidneys remain effective "guardians of the internal environment" so long as enough water reaches them.

The most desperately ill cases with massive edema almost invariably showed evidence of severe dehydration, and complained of extreme thirst. The water of the first few intravenous injections was used to bring all of the body fluids up to a normal dilution and to relieve the water deficit of the cells. During this period there often was no diuresis, some gain in weight, and sometimes a visible increase in the edema. Coincidentally, however, there was usually such marked clinical improvement as to encourage continuation of treatment, and usually there ensued a diuresis and the disappearance of the edema. *Mercurial diuretics* were employed infrequently to

speed elimination when the degree of edema was a major cause of discomfort. When they were used, the water intake was increased to a maximum to avoid the danger of postdiuretic dehydration and shock.

Patience and ingenuity are required to administer large amounts of water to the very ill. When the oral route became possible, a tedious insistence often was necessary to bring the oral intake to the point where it was wise to discontinue intravenous administration. Prescribing a few drops of dilute *hydrochloric acid*, *peppermint water*, or a half teaspoonful of *wine* to be taken in a glass of water every hour, or even half hour, from morning until about six o'clock at night, was found very effective in keeping up the intake.

In regard to the prognosis for life, 40 of 102 patients who were started on the high fluid regimen more than five years ago are still living, a survival rate of 39 per cent. Whereas, in the series of 150 cases of congestive failure reported by Dry (1942), treated by accepted methods with restriction of fluids, 40 were living after five years, a survival rate of 27 per cent. The comparison in favor of the high fluid regimen seems more than fair since 74 cases (72 per cent of the 102 cases) showed massive anasarca when first seen five years ago, and in 22 (21 per cent) the onset of congestive failure preceded institution of the high fluid regimen by an average of 6.3 (2 to 15) years.

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## GASTROENTEROLOGY

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### Stomach

**Peptic Ulcer** — The importance of this condition in military medicine has been clearly evident during World War II and a very complete analysis of 340 proven ulcer patients admitted to the Gastrointestinal Section of the Tilton General Hospital was presented by Berk and Frediani.<sup>1</sup> Proven gastroduodenal ulcer made up 40 per cent of the admissions to the gastrointestinal section and this figure approximated reports from other centers and countries. Figures on the existence of symptoms before army service vary from 50 to 95 per cent. In

the series reviewed, three fourths (74 per cent) presented symptoms which would indicate the existence of ulcer prior to induction. The duration of symptoms before induction varied from eight weeks to twenty years, or an average of about five years. Over one half of these claimed they had informed their induction board of their digestive distress. The average length of service before hospitalization averaged only seven and one-half months and the average number of days spent in hospitals for the last recurrence of ulcer was 51.5 days in station hospitals and 43.9 days

at Tilton General Hospital. The recent disposition of proven ulcer cases has been to return to a restricted type of duty those soldiers with an uncomplicated ulcer, whose symptoms first appeared while in the service or who possess some skill or ability that might prove of value to the army.

Berk and Frediani presented further clinical data. The average age of their cases was twenty-nine and one-half years and, interestingly, Hebrews comprised only 4 per cent of the entire group and Negroes made up 4.4 per cent. Duodenal ulcer occurred fifty times to one gastric ulcer or in 98.7 per cent of all ulcers. Only one jejunal ulcer was observed. An ulcer niche or crater was seen in only 26.6 per cent of the cases which presented roentgenographic abnormality. This absence of frequent direct positive x-ray evidence of ulcer is understandable because by the time the cases reach a general hospital they have first been seen and treated in other hospitals. Over one half disclosed a hyperacidity by the fractional Ewald meal gastric analysis with readings of fifty or more clinical units of free acid. Only 6.7 per cent had a grade III hyperacidity (a maximum free acid of eighty-five or more clinical units) and in only 1.7 per cent was it grade IV (a maximum free acid of 100 or more clinical units). Abnormal motility was present in 36 per cent with hypermotility in 8.5 per cent and hypomotility in 27.5 per cent. Concerning the character of symptoms, these authors observed that at least 10 per cent (particularly the young) give an atypical ulcer history but this tends to become more clear cut and the symptom complex more like the classical one as it is retold. In treatment, it was found necessary to use antacids for the relief of pain in only 18 per cent of their cases. Psychosomatic features were observed to

be the most important factor in the management and disposition of these cases. Many times there was a remarkable coincidence between the onset of distress and some unpleasant episode. However, according to these authors, "the aggressive, driving, conscientious, punctilious, perfectionist type of personality that is so commonly observed in civil life was seen relatively infrequently in soldiers with peptic ulcer. The slovenly, seemingly placid, unobtrusive, slow-moving men were seen far oftener." In this series, 17.7 per cent were complicated by hemorrhage at one time or another; 7.6 per cent developed perforation and 3.1 per cent pyloric obstruction.

**Treatment**—A. C. Ivy,<sup>2</sup> by the parenteral administration of a *mucosal extract* from the upper intestine of swine, has succeeded in preventing the occurrence of gastrojejunal ulcer in a high percentage of Mann-Williamson dogs and this protection is not limited to the period during which the extracts are being administered but has so far been observed to extend for periods as long as three years after cessation of treatment. His preliminary results on the treatment of human peptic ulcer patients with this "enterogastrone concentrate" are sufficiently encouraging to warrant further study to ascertain its value in the prevention of recurrences. To date only some fifty such cases have been followed but the results, as time passes, seem very favorable in the control of the most difficult ulcer problem, namely, the prevention of recurrence.

**Treatment with Amino Acids (Amigen)**—In the course of studies on the effect of a hyperalimentation regimen with high caloric and high amino acid feedings on convalescence after gastrectomy, Co Tui and associates<sup>3</sup> used this program on four peptic ulcer patients preoperatively with striking clinical im-



provement. Twenty-six additional patients were included in the report. There were twelve cases of duodenal ulcer, five combined duodenal and gastric ulcer, seven gastric ulcer, one suspected marginal ulcer, and one marginal ulcer in the series. The length of ulcer history varied from one month to twenty years; fourteen were intractable cases which had not responded to strict treatment previously. Six patients had had profuse hemorrhage, and six had gastric retention varying from 20 to 100 per cent. The patients received two hourly feedings of *amino acids* (amigen) and *dextrimaltose*. This mixture contained from 0.5 to 0.8 gm. of nitrogen and 40 to 50 calories per kilogram of body weight per twenty-four hours. For a 60-kilogram man, the amount of amigen taken in twenty four hours was from 300 to 400 gm., with a nitrogen content one and one-half to three times that of a high protein diet. The mixture was given exclusively for from two to three weeks, depending upon the subsequent x-ray findings. If, after two weeks, the x-ray examination indicated healing of the ulcer, the patient was given a bland diet supplemented by two hourly feedings of amigen. Supplementary *vitamins* were included in the program and consisted of thiamine, 50 mg.; ascorbic acid, 100 mg.; riboflavin and niacin, each 50 mg. Liver extract, 15 U.S.P. units, was given intramuscularly twice a week.

The results of this treatment were striking. Pain was relieved within twenty-four hours in fourteen patients and in forty-eight hours in thirteen patients. Seven of these patients had formerly had intractable pain. Vomiting stopped in twenty-four hours. Gastric acidity and *pH* determinations in eighteen patients showed a definite tendency to lowered free acid with increased *pH* after feedings which was maintained for two to

three hours. All of the patients gained weight during the treatment. Check x-ray studies revealed rapid decrease in irritability and healing of the ulcers in those cases in which craters were visualized.

A further report on the use of amino acids in *bleeding peptic ulcer* was made by Levy.<sup>4</sup> This writer commented upon the fact that "the importance of the hypoproteinemia which results from massive gastroduodenal bleeding has received only scant attention." The effect of hypoproteinemia on wound healing has been demonstrated in many other conditions and experimentally. "The disturbance in the body metabolism generally and in the repair of damaged tissue in particular are important factors in any disease process. In a bleeding peptic ulcer, this is as important as in any other pathological condition." It is suggested that plasma protein levels be added to any criteria for the purpose of grading the degree of hemorrhage in accordance with the following table:

Grade I.....	6.50 gm. or more plasma protein
Grade II....	6.49 to 6.00
Grade III.....	5.99 to 5.5
Grade IV.....	5.49 or below

This classification in addition to red cell and hemoglobin determinations and the apparent clinical condition of the patient proved satisfactory in the author's experience. On admission, blood was taken from each patient for the determination of the red cell count, hemoglobin, white count, and differential, hematocrit, nonprotein nitrogen, and serum protein. These studies were made daily. Transfusions of *plasma* or whole blood were given when indicated for shock, or when the hemoglobin and red cell count fell below 35 per cent and two million respectively. As soon as the bleeding stopped, which was usually within twenty-four hours from the time

of admission, 10 per cent *amigen* in 10 per cent *glucose* was given orally in addition to hourly Sippy feedings. The mixture was given as a constant drip through a Levin tube or in amounts of 90 cc. every hour as a substitute for the alkali in the Sippy regimen. The patient usually received 100 gm. of amigen per day, although it was increased in those in whom a satisfactory rise in serum protein did not occur. A maximum of 300 gm. was given in one day. The addition of 0.5 per cent salt and vanilla extract improved the taste of the solution.

Seventeen cases were reported, eleven of which received amigen, while the remaining six served as controls. In this control group, the serum protein returned to normal in an average of 19.5 days, while in the amigen-treated group normal levels were reached in from ten to twelve days. Clinically, the amigen-treated patients seemed to do better than the control group in spite of the fact that there were more cases with severe hemorrhage in this group.

The *intravenous* administration of amino acids (amigen) has been suggested as a valuable adjunct in the postoperative management of gastrointestinal cases. It has been noted that rapid injections of this material may produce nausea and vomiting. Experimental work by Learner *et al.*<sup>5</sup> showed that rapid injection resulted in duodenal hypermotility or change of pattern in anesthetized dogs. This was found not to be associated with changes in pH, CO<sub>2</sub>, Cl, or total base of the blood plasma. Neither hypermotility nor hyperglycemia were prevented by atropine or vagotomy. Rapid injections in humans changed the character of contractions and often accentuated tonus changes. Subjective sensations and changes in

motility were correlated in only half the cases studied.

A timely reminder that the patient who has undergone a partial gastrectomy often still needs medical care was thoroughly discussed by Berkman and Heck.<sup>6</sup> They conceded that *partial gastric resection* is the best surgical treatment of gastroduodenal ulceration that has so far appeared, but pointed out that there are other complications beside recurrent ulceration. Although the latter condition is infrequently seen and the mortality rate correspondingly low in competent hands, there are still patients having gastrointestinal symptoms following removal of the ulcer-bearing area, some of whom are incapacitated to a degree far greater than some patients who have only the misfortune of having recurrent ulceration. These annoying sequences which may follow subtotal gastrectomy are as follows:

1. Distressing gastrointestinal symptoms:
  - (a) Postprandial symptoms or the so-called dumping syndrome.
  - (b) Inanition resulting from postprandial distress.
  - (c) Nausea unassociated with postprandial symptoms or the ingestion of food.
2. Inability to regain weight lost at time of operation.
3. Persistent hypochromic microcytic anemia which may or may not be associated with postprandial distress or with inanition.

The postprandial distress seen in the dumping syndrome is brought on by the administration of food and occurs rather abruptly either before the meal has been completed or immediately thereafter. According to these authors, nausea is severe and may produce the picture of mild shock, but actual vomiting is rare. Diarrhea, consisting of four to six stools a day, may present a problem. However, in the majority of the cases, the severity of all these symptoms abates in a matter of months or, in less fortunate cases,

results in a more annoying state of inanition.

Berkman and Heck commented that the inanition resulting from postprandial symptoms sets up an anorexia and aversion for food very similar to the problem confronted in the treatment of anorexia nervosa. These authors believed that the general practice of keeping patients, who have undergone partial gastric resection, on diets of soft and nonirritating foods is continued too long. They considered it advisable to substitute three meals daily for the accepted regimen of frequent (six) feedings of a soft or ulcer diet as soon as possible and to increase the number of calories gradually. As a rule, their patients were given a three-meal program at about six weeks after gastric resection. Bulk is usually avoided in gastroenterology but these writers pointed out that the bulk of the diet, through moderate distention of the stomach at mealtime, appeared to have something to do with the maintenance of comfort and the prevention of a sensation of fulness and distention after meals. Obviously, then, after partial gastric resection when the capacity of the stomach is decreased by a half or more, fulness and distention will occur after ingestion of even small amounts of food and much more quickly than it does in a stomach of normal capacity. Thus, by starting with a comparatively small amount of bulk in a diet served in three daily meals and by gradually increasing the bulk of the diet, this sensation of fulness and distention will be either greatly decreased or will disappear.

The three-meal regimen and increasing bulk worked very nicely in the management of a number of patients who had no particular postoperative distress, but who were unable to increase their weight.

Many workers report perniciouslike anemias, hypochromic anemia, or a combination of the two following gastric resection. Berkman and Heck discussed the hypochromic anemia which develops postoperatively without a demonstrable cause and which does not respond to the accepted methods of handling that type of anemia. They presented one case which had had large doses of iron, liver, and vitamins without improvement until placed on the dietary program previously discussed and they, therefore, assume that there exists a nutritional defect of some kind.

**Carcinoma of Stomach**—Despite modern aids to diagnosis, the salvage rate for patients with carcinoma of the stomach is but 2 per cent, according to Rigler *et al.*,<sup>7</sup> who attribute this poor figure largely to late recognition of the lesion. The major factors leading to failure in diagnosis are the insidious onset, absence of striking symptoms even in advanced tumors, and difficulties in establishing the diagnosis.

Previous reports indicate that not more than 3 persons in 1000 over the age of forty are likely to have cancer of the stomach at any one time. Investigation of symptomless persons over age fifty showed only 3 tumors in 2400 cases. The authors call attention to the relatively high incidence of coexisting *cancer of the stomach and pernicious anemia*. This relationship has shown apparent increase in the past twenty years probably due to better recognition and to the increased longevity of persons with primary pernicious anemia. However, this association raises certain questions: Is the association accidental in two diseases occurring in the same age group? Does carcinoma of the stomach produce a pernicious anemia-like picture or true pernicious anemia or does pernicious anemia produce cancer of the

stomach? Is there a common precursor for the two diseases which tends to produce either or both diseases?

Kaplan and Rigler previously reported 293 cases of pernicious anemia in 43,021 consecutive autopsies in persons over forty-five years of age. In this group there were thirty-six cases of carcinoma of the stomach, an incidence of 12.3 per cent; three times as great as in the remainder of the series in the same age group. It was formerly thought that chronic gastritis was the precursor of both diseases but recent evidence questions this conclusion. There is evidence of a hereditary or familial tendency toward both of these diseases.

In the present report, 211 patients with pernicious anemia were carefully studied by x-ray. Carcinoma of the stomach was found in seventeen cases (8 per cent) and benign tumors in fifteen cases (7.1 per cent). In the course of these studies several observations were made: Apparently benign tumors changed to malignant ones; some cases showed a progression from pernicious anemia through gastric polyps to a full-blown gastric carcinoma; a moderate or large carcinoma was not infrequently found in patients without any gastric symptoms; patients with pernicious anemia showed a tendency to develop gastric tumors.

The authors recommend that semi-annual x-ray examinations be made on patients with pernicious anemia in an effort to make early diagnoses.

### Small Intestine

**Regional Ileitis—*Clinical Management***—Kiefer and Ross<sup>8</sup> carefully reviewed 107 cases of ileitis at the Lahey Clinic in Boston and discussed 11 patients who had the disease in the early acute state. This was proved in every case by laparotomy, at which the sur-

geon reported inflamed, edematous, and thickened loops of small intestine and acute lymphadenitis in the mesenteric nodes. Seven of these cases had roentgenological examinations just before operation and one just a few days after abdominal section. Five of these showed variations from the normal appearance of the small intestine mainly as follows: (1) Some hypermotility in the small bowel; (2) somewhat widely separated loops of terminal ileum suggesting thickening of the intestinal wall and mesentery; (3) unusually long segments of pronounced spasm; (4) irregularities of the mucosal pattern suggesting edema of the mucosa with flattening and rearrangement of the folds. These findings are of significance because they offer a means for the internist to make a diagnosis of acute ileitis without the necessity of an exploratory operation.

In this review of 107 cases, the following incidence of symptoms was observed: Pain, 92 cases; malnutrition with weight loss, 80 cases; fever, 65 cases; diarrhea, 60 cases; external fistula, 23 cases; abdominal mass, 40 cases, and anemia, 42 cases. The authors pointed out the value of repeated x-ray examinations and the importance of even slight variations from the normal pattern, particularly if the distortions are constant in serial roentgenograms.

It was pointed out by these authors that as the complications of the disease manifest themselves, the diagnosis is more easily made. Thus, as partial or complete obstruction of the small gut develops, the abdominal symptoms become more severe and the x-ray picture is more obvious. Stasis and small bowel dilation are the outstanding features and may be quite pronounced with or without demonstrating the characteristic areas of narrowing or rigidity. The other complication of fistula formation usually pro-

duces striking roentgenological effects which are strong presumptive evidence of ileitis.

Concerning the management of chronic ulcerative enteritis, Kiefer and Ross believed it dependent upon: (1) State of the morbid process; (2) location and extent of involvement in the small intestine; (3) activity of the inflammatory, ulcerative, and cicatrizing process; (4) complications. They also suggest the following five classifications of cases according to clinical groups to allow of better management: (1) Early acute enteritis without complications; (2) chronic terminal ileitis without complications; (3) chronic terminal ileitis without obstruction or perforation; (4) extensive segmental ileojejunitis without complications; (5) extensive segmental ileojejunitis with complications.

In group 1, operation is to be deferred unless acute appendicitis is probable. In cases falling into group 2, a medical regimen should be given a trial, but in the majority of cases surgery will become necessary and will probably consist of resection of the terminal ileum and ascending colon. In the third group with obvious perforation or obstruction, the procedure of choice is an ileo-ascending colectomy. The fourth group of extensive uncomplicated ileojejunitis is extremely hard to manage and because of the extensive involvement, even surgery has little to offer. Therefore, supportive medical management is to be preferred. In the fifth group of complicated ileojejunitis, surgical measures must be performed.

**Etiology and Pathology**—Schepers,<sup>9</sup> of Johannesburg, South Africa, presented an extremely thorough and comprehensive review of the problem of so-called regional ileitis and expressed some new thoughts concerning the pathology of the disease. First of all, he

lamented the poor nomenclature of the disease for no one term defines this complete condition which may affect virtually any part of the intestinal tract and may ultimately involve all parts of the abdominal cavity as originally described by Crohn in 1932 and 1939. He considered it wiser to retain the present more popular name—regional ileitis.

Concerning epidemiology, he observed the lesion to be about half as frequent in its incidence as ulcerative colitis and that it shows no racial preference. It seems more prone to arise in the second decade of life and most records indicate that more males are involved. Acute cases may undergo spontaneous cures, but when the condition has become chronic, recovery can only be effected by surgical resection and recurrence may be expected in 7 to 20 per cent of the cases.

The theories concerning the cause of the condition were carefully discussed. Owing to the manifest inflammatory nature of the lesion, diligent search was made in the past decade for an infective etiological factor. To date there has been nothing proven with the various organisms discussed, particularly the tubercle bacillus, *B. coli*, or streptococcus viridans. Likewise, no positive findings came from a study of the biochemical or biophysical etiological factors, although the author admitted this possibility had not been properly explored. Trauma, which may be manifest in many ways, including the ingestion of foreign bodies or local irritation from mechanical defects, may conceivably set up a slow necrosis, inflammation, and repair; but this will not explain all the cases. Similarly, the only remaining theory of lymphatic block has been discredited by many of the writers.

Schepers discussed the various clinical features and observed an acute phase

characterized by peritoneal irritation with pain in the iliac fossa, fever, and spasm which soon settled down to three chronic phases which were described. The first phase is associated with diarrhea and the passage of mucus and sometimes blood; cramps without tenesmus; perianal lesions; bouts of fever; weakness and loss of weight. After one to fifteen years, the second chronic state appears as stenosis supervenes. The clinical features are those of chronic partial intestinal obstruction — namely, colicky abdominal pain, distention, nausea, and vomiting, and constipation alternating with diarrhea. The last phase is associated with fistula formation which may occur early and so complicate the picture that the original diagnosis becomes difficult. The presence of a palpable mass, particularly in the right iliac fossa, associated with some of the above symptom complex and a "string sign" of Kantor warrants a diagnosis of regional ileitis and usually necessitates laparotomy and surgical resection.

In the second part of his monograph, Schepers described in minute detail the pathologic findings in a typical case of regional ileitis and paid particular attention to the micropathology involved. On this basis he divided the disease into two components: A *primary* phase characterized by: (1) A stage of edema of the submucosa and serosa with dilatation of submucosal lymphatics and hyperemia of juxtamuscular adventitial blood vessels; (2) a stage of plasma cell infiltration of the submucosa and serosa; (3) diffuse fibrosis, with disappearance of the plasma cells, except where trapped, and (4) healing. The *secondary* phase is characterized by ulceration superimposed on any of these phases of the primary lesion, with corresponding modification of the pathologic process. There are

tendencies to early or late perforation, fistulation, and granuloma formation.

Schepers presented a critical discussion of the possible etiological factors and suggested that the primary disturbance may be due to either acute injury to the bowel wall by a metabolite, probably lipoid in character, or result from a neuropathic disturbance involving Auerbach's and/or Meissner's plexuses, or mesenteric and celiac ganglia. He stated that the original neuropathic lesion is possibly a type of visceral herpes zoster and suggests that the chronic type of secondary ulceration only occurs when ganglionic lesions are not only irritative but destructive, and thus lead to denervation of the affected bowel wall. To further support this theory, he commented how the progression, distribution, and characters of the secondary chronic lesions are much like those around the spreading mycelium of fungal lesions and the early acute reaction resembles the manifestations of certain virus diseases. As a final stimulus, he suggested that extensive search be made for the same sort of virus factor as that causing herpes zoster or, as recent correlations suggest, regional varicella.

### Liver

**Hepatitis**—The increased interest in epidemic jaundice (infectious hepatitis, infectious jaundice) is indicated by the large number of contributions in recent literature. Although not a new disease, the increased incidence under wartime conditions has renewed interest in its etiology, pathology, and treatment. While most of the literature deals with military personnel, there has been a noticeable increase in civilian reports in the past two years. Stowman<sup>10</sup> states that in Europe, published figures indicate an incidence of from 1 per cent in Norway to 4 per cent in some of the provinces.

The mortality rate in recorded series has been from 0.1 to 1.0 per cent. In the Mediterranean theater of operations, the disease became of military importance because of the relatively high incidence and the resulting prolonged disability.

Barker and associates<sup>11</sup> collected studies on 1172 unselected cases. In their opinion, the disease is caused by a filterable virus which may be transmitted by subcutaneous or intravenous routes (vaccination, transfusion) or orally. The pathology is primarily in the parenchymal hepatic cells with some inflammatory exudate in the periportal areas. These authors describe a type of the disease not associated with clinical icterus which they believe was at least as frequently seen as the typical cases. By means of a series of liver function tests, these nonicteroid cases were found to run a similar course, differing only in the lack of bilirubin retention.

The clinical features of classical infectious hepatitis, or catarrhal jaundice, are well known and need not be reviewed at this time.

It was found that too early exercise during the convalescent stage was very prone to induce a relapse. The first indication of relapse is the recurrence of a large tender liver. The average case requires six to eight weeks for recovery. From 5 to 10 per cent of the cases are not clinically well at the end of three months, however.

**Etiology and Epidemiology**—RELATIONSHIP BETWEEN SERUM JAUNDICE AND INFECTIOUS HEPATITIS—The occurrence of postvaccinal jaundice early in the war stimulated research as to the causative factor or factors. This work was reviewed by Paul *et al.*<sup>12</sup> in connection with transmission experiments in serum jaundice and infectious hepatitis. These writers consider these two conditions to be similar but experiments

have not proved them to be identical. Homologous serum jaundice may result from various sera used for prophylaxis (measles, mumps) and vaccines (yellow fever). The active agent has not been isolated but it has been proved to be filterable and heat resistant (130° F. [56° C.] for one hour). It produces jaundice in humans when given parenterally. The incubation period is long (70 to 100 days or more). Transmission has been reported by oral feeding of serum and of nasopharyngeal washings.

Using an icterogenic agent derived from a serum pool collected from troops in Egypt, the authors demonstrated that of twenty-three individuals receiving variable amounts of serum from volunteers who had been previously vaccinated with the original serum, ten developed jaundice in from 50 to 135 days. This transmission of the virus obtained from serum is similar to the experience with the virus from acute infectious hepatitis. This latter virus has been passed serially to man (two passages). It resists heat of 130° F. (56° C.) for one half hour and will pass bacteria-tight filters. It is present in feces and urine and may be transmitted to man by the oral route. Havens *et al.* had previously shown that when fecal material from patients with naturally occurring infectious jaundice was fed to human volunteers, two out of three contracted the disease in twenty and twenty-two days respectively. The serum from these two patients in the preicteric phase was filtered and heated and fed to five volunteers, four of whom developed jaundice after twenty-three to thirty-four days. The same material injected parenterally produced jaundice in six of eleven volunteers after an incubation period of from twenty to thirty-one days. Some of these latter volunteers had recovered some months before from

serum jaundice, but this did not protect them against infectious hepatitis.

The difference in incubation period between serum jaundice and infectious jaundice has not been explained.

Further studies on the relationship between the virus of infectious jaundice and serum jaundice by Neeffe *et al.*<sup>13</sup> showed that pooled specimens of feces from patients with serum jaundice administered to nineteen volunteers failed to produce a single case of jaundice. Feces from patients with infectious hepatitis, however, produced jaundice in six of twelve volunteers within twenty-six days.

Epidemiological data was obtained by Neeffe and Stokes<sup>14</sup> during an epidemic of infectious hepatitis in a summer camp. They demonstrated that the source of infection was contaminated well water. Three hundred and fifty patients of a total camp census of 572 developed hepatitis. In 344 of these 350, the disease had its onset within a period of 7 weeks. Two hundred fifty-five had clinical jaundice, 95 a nonicteric form of hepatitis. Careful epidemiologic data indicated that the transmission of the disease was by fecal contamination of well water and not by air, fomites, biting insects, food, milk, lake water, or directly from infected persons.

Transmission experiments were conducted upon volunteers using serum, nasopharyngeal washings, urine, feces, fly extracts, and water from the contaminated well. The results indicated that the icterogenic agent was not present in the nasopharyngeal washings or urine of this group of patients. Oral administration of serum and feces of active cases produced hepatitis in nineteen to thirty-seven days. Parenteral administration of the materials did not reproduce the disease.

Subsequent experiments<sup>15</sup> on disinfection of the contaminated water showed that chlorination to provide chloride residuals of one part per million did not inactivate or attenuate the causative agent. Stronger chlorination (fifteen parts per million) after thirty minutes contact attenuated the agent. Treatment of contaminated water with sodium carbonate, aluminum sulfate, and activated carbon did not completely inactivate the agent. The authors concluded that the complete inactivation of the causative agent in drinking water may require further modifications of methods used for water disinfection.

*Accidental transmission by syringe* of the agent of infectious hepatitis was reported by Droller.<sup>16</sup> There were sixty-three cases of acute hepatitis in patients attending a diabetic clinic in England. Epidemiologic studies indicated that while some cases may have resulted from contact between patients, there was conclusive evidence that some of the cases resulted from contaminated syringes.

*Clinical studies* on cases of serum jaundice were reported by Rappaport.<sup>17</sup> There were thirty-three patients in the series, all of whom developed hepatitis after receiving pooled plasma following war wounds or serious illness. Thirty-one had clinical icterus, two presented evidence of hepatitis without jaundice. No cases of jaundice were seen in the hospital during this period except those who had previously received plasma and there were no cases of secondary spread to other patients. The incubation period varied from 63 to 126 days. The clinical picture was identical with so-called catarrhal jaundice. All showed early evidence of reduced hippuric acid secretion. The Hanger cephalin-cholesterol flocculation test was strongly positive in twenty-five of thirty-one cases at the peak of jaundice, falling to normal in three to



four weeks despite persistence of icterus in some. The ester cholesterol fraction was reduced in fourteen of twenty-two cases. Galactose tolerance was normal in five of twelve at the peak of jaundice. Sulfobromophthalein (5 mg. per kilogram) was used after the icterus had subsided. In only four of eighteen was there dye retention up to 5 per cent in thirty minutes, the remaining fourteen showed no retention. Plasma proteins frequently were reduced in this series. Prolonged prothrombin time was demonstrated in only one case.

**Use of Gamma Globulin for Prevention and Attenuation of Infectious Hepatitis**—Stokes and Neefe<sup>18</sup> observed that the incidence of jaundice in patients receiving gamma globulin for prevention of measles was greatly less than in those receiving blood, plasma, or serum. "Because the evidence thus far available suggests that the virus agent responsible for epidemic or infectious hepatitis is present in the blood during the preicteric and early icteric phases of the disease, it seemed reasonable to postulate that such neutralizing antibodies in gamma globulin might possibly be effective in aborting or in attenuating this disease if administered during the incubation period or preicteric stage."

In an epidemic of infectious hepatitis at a girls' camp in August and September, 1944, 0.15 cc. of gamma globulin was given per pound of body weight to 53 persons of a group of 331 exposed to the disease. The incidence of hepatitis in the injected group was significantly lower than in the controls (20.8 per cent as compared with 67 per cent). In three cases given gamma globulin who developed icterus it lasted only four, five, and seven days respectively, while the average for controls was 14.2 days, suggesting attenuation of the virus.

A subsequent report by Gellis *et al.*<sup>19</sup> added support to the above conclusions. A bombardment group having a high incidence of hepatitis was used for study. Two squadrons received 10 cc. of gamma globulin per man and two squadrons were held as controls. There were about 1000 men in each group. In the squadrons receiving globulin, only 3 cases of hepatitis developed in the subsequent seven weeks, while in the control group there were 25 cases.

In a larger group of ground forces in the Mediterranean Theater, 1732 men received 10 cc. of gamma globulin intramuscularly, while 10,326 in the same units were used as controls. The incidence of jaundice in the injected squadrons was between 0.4 and 1.0 per cent, while in the controls it was between 2.0 and 3.7 per cent in various groups.

Havens and Paul<sup>20</sup> used gamma globulin in an outbreak of infectious jaundice in a children's home. Ninety-seven susceptible children were given gamma globulin (0.06 to 0.12 cc. per pound); 155 children were kept as controls. In the injected group, the incidence of jaundice was 2 per cent, while in the controls it was 23 per cent. Questionable hepatitis without icterus occurred in 6 per cent of the injected group and in 11 per cent of the controls.

Further studies were conducted by Gellis *et al.*<sup>21</sup> in a service hospital during an epidemic of infectious jaundice. Alternate patients admitted to the hospital with preclinical jaundice were given 0.3 cc. of gamma globulin per pound, an average dose of 45 cc. Two hundred seventy-eight patients were admitted; 70 developed jaundice; the majority of the remainder proved to have hepatitis without jaundice as indicated by liver function tests. Of the jaundice group, 31 had had globulin; 39 were controls. There was no clinical or laboratory evi-

dence that the globulin altered the clinical course.

**Gamma Globulin in Posttransfusion Hepatitis**—During 1944-45, a large and increasing number of cases of acute hepatitis were seen in a large Army general hospital in this country which dealt primarily with amputation and neurosurgical cases. Grossman *et al.*<sup>22</sup> studied a series of 108 cases, 103 of which occurred in men recently wounded. While 95 per cent of the jaundice cases occurred in battle casualties, this group made up only 44 per cent of admissions to the hospital. The time elapsed between injury and jaundice varied from 44 to 167 days with an average of 92.6 days. The large majority had received whole blood or plasma or both shortly after injury. The mortality rate was 2 per cent. The relative incidence of jaundice in patients who received no blood or plasma was 0.3 as compared with 9.5 per cent in those who had received blood or plasma or both.

The effect of administration of gamma globulin on the incidence of jaundice in the group of casualties was studied by giving 10 cc. of human immune serum globulin on admission and again in one month. The incidence of hepatitis developing more than one week after admission was 1.3 per cent in the injected group as compared with 8.9 per cent in the controls. The similarity between these results and those obtained by the use of gamma globulin in acute infectious hepatitis suggests that the agent from these blood products producing hepatitis is the same agent as that occurring in epidemic hepatitis or that antibodies protective against more than one agent producing hepatitis have been concentrated in the globulin from large pools of plasma. The evidence to date indicated that early administration of human immune serum globulin was effective in

preventing hepatitis in this series of cases.

Later studies by Stokes *et al.* have failed to substantiate the preventive action of gamma globulin on homologous serum hepatitis following blood or plasma transfusions. Experimental work also failed to show neutralizing antibodies in gamma globulin against the icterogenic substance in plasma in one series of experiments. The reasons for the difference in results is not apparent.

**Gastroscopic Observations in Infectious Hepatitis**—Knight and Cogswell<sup>23</sup> reported gastroscopies on nine patients with infectious hepatitis. In seven cases the mucosa showed abnormal changes consisting of superficial gastritis involving primarily the antral area and in five cases this was associated with aphthous ulcers.

**Treatment of Hepatitis**—In spite of the increased interest in hepatitis, there have been few publications regarding treatment of this disorder. Most writers agree that a program should include bed rest, a diet rich in protein and carbohydrate and poor in fat, and administration of multivitamin products, especially ample B complex.

**Methionine** has been found to be of apparent value in some cases of hepatitis. Eddy<sup>24</sup> reported the use of this amino acid in thirty cases of acute toxic hepatitis, most of which were due to trinitrotoluene. Ten of the patients were seriously ill. There were no fatalities in this series as compared with the published mortality of TNT hepatitis of 30 to 35 per cent. In two cases seen prior to the use of methionine, one was fatal and the second had a long convalescence. In addition to the general program as given above, the author administered 3 to 8 gm. of methionine daily. Improvement usually was noted promptly. In two cases of epidemic hepatitis, there

was marked improvement within forty-eight hours. No toxic reactions were encountered.

The author reviewed the literature leading up to the use of methionine in treating acute hepatitis. Miller, Ross, and Whipple in 1940 demonstrated that the amino acid, methionine, and, to a less extent, cystine gave protection against liver injury if given before chloroform anesthesia. Later, in 1942, these workers showed that protein-depleted animals could be protected against chloroform anesthesia damage even when methionine was given three to four hours after exposure to chloroform. The manner in which methionine protects the liver is not clear but there is evidence to support the belief that its value depends primarily on the sulfur content of the amino acid. Gyorgy, in 1944, reviewed the work in this field and suggested that the protection afforded by choline plus cystine might be explained by their necessity for the synthesis of another substance which might be methionine.

**Disability Following Postvaccinal Hepatitis**—A group of 200 patients showing prolonged convalescence after postvaccinal hepatitis (five to nine months) was studied by Benjamin and Hoyt.<sup>25</sup> It was found that 11 per cent had some retention of sulfobromophthalein dye after thirty minutes. Improvement in liver function was noted to be continuing at the end of six months to a year. In 18.5 per cent of these patients, a vasomotor disturbance was found and was manifested by tremor, icy cold, red, dripping hands and overpowering weakness. This group showing prolonged convalescence represented only a small proportion of the soldiers originally suffering from postvaccinal hepatitis.

**Liver Function Tests**—**METHYLENE BLUE**—A test of bilirubin in urine by use of methylene blue was suggested by

Franke in 1931 and modified by Fellinger and Menkes in 1933. Stokes and Neefe<sup>9</sup> and Gellis and Stokes<sup>26</sup> found the test of value in the study of cases of infectious hepatitis. The latter authors reported the use of the test in seventy-seven patients with hepatitis and jaundice. It was found that in thirty-three patients developing jaundice after admission, the test became positive one to six days prior to the appearance of the icterus and in twelve of these patients it was positive before the icterus index was elevated. The test became negative after the peak of jaundice was reached even though clinical icterus and an elevated icterus index persisted.

In five patients who developed relapses, the methylene blue test and the cephalin-cholesterol flocculation test again became positive preceding the clinical evidence of relapse.

**Method**—To 5 cc. of prebreakfast urine was added two drops of a 0.2 per cent aqueous solution of methylene blue chloride. If a green color resulted, more methylene blue was added dropwise and the last drop required to convert the green color to blue was recorded. A test of five drops or more was considered positive. If more than five drops were needed, the urine was diluted with distilled water to aid in determining the end point. The mechanism of the test is uncertain.

The authors concluded that the test was of value in the early diagnosis of preicteric hepatitis; in evaluating the course of the disease; and in the prediction of impending relapse.

**COMPARATIVE VALUE OF SEVERAL LIVER FUNCTION TESTS**—According to Teitelbaum *et al.*,<sup>27</sup> "the present dissatisfaction with liver function tests is largely dependent upon a tendency to rely solely upon the result of one particular liver function test, disregarding such factors as the multiple functions of the liver, its regenerative ability, or the type of injury. It is obvious that in an organ with multiple functions, such as the liver, the result of a single test may be negative in the face of damage

so extensive that it can be ascertained without any laboratory procedures. Such a negative result means only that the test chosen measured a function not as yet altered in that particular diseased liver. The value of any single liver function test, when used, is directly proportional to an appreciation by the user of the function it is testing."

Eight different liver function tests were performed on each of 153 patients with various types of suspected liver disease.

**Methods and Results**—1. **Urinary Urobilinogen Test**—A modification of the method of Wallace and Diamond was used. Distilled water is added to fresh urine to make dilutions of 1:10, 1:20, 1:40, 1:80, etc. To 25 cc. of each of these dilutions is added 2 cc. of Ehrlich's reagent. Readings are made in five minutes, looking down through the tube. A pink color appears in positive cases and is normally rarely seen in above 1:20 dilution. A 1:40 positive was considered a positive test.

In fifty-seven cases, 75.4 per cent showed abnormal secretion:

Cirrhosis	....41 patients	82.9 per cent positive
Neoplasm	.... 6 patients	66.7 per cent positive
Hepatitis	....10 patients	50.0 per cent positive

2. **Van den Bergh Reaction**—In fifty-eight cases of liver disease, the quantitative Van den Bergh was positive (over 0.7 mg. per cent) in 51.7 per cent. In this group there were twenty-one direct, nine delayed direct or biphasic reactions. The incidence of positive tests ranged from 81.8 per cent in hepatitis to 66.7 per cent in neoplasm and 41.5 per cent in cirrhosis.

3. **Galactose Tolerance Test**—The method of Shay, Schloss, and Rhodis was used. A fasting urine specimen was examined for sugar, then 40 gm. of powdered galactose were given orally and urine specimen collected hourly for

five hours. No food was given during this period. A total five-hour elimination of 3 or more gm. of galactose was considered an indication of hepatic disease. In this series a positive test was obtained in 30 per cent of cases of hepatitis, 18.4 per cent of cases of cirrhosis, and 16.7 per cent of cases of neoplasm.

4. **Glucose Tolerance Test**—In extreme hepatic disease, glycogen storage frequently is disturbed with a resulting diabeticlike curve but with low fasting sugars and frequent hypoglycemia during the third to fifth hours. Using 1.75 gm. of glucose per kilogram of body weight, the authors found abnormal curves in 70.4 per cent of fifty-four patients with hepatic disease:

Hepatitis	.....	90.0 per cent abnormal curves
Neoplasm	.....	66.7 per cent abnormal curves
Cirrhosis	.....	65.8 per cent abnormal curves

In 25.9 per cent, the fasting blood sugar was normal and the test produced no glycosuria or hypoglycemic reactions.

5. **Serum Proteins**—Total protein concentration under 6.5 gm. per cent and serum albumin under 4.0 gm. per cent were considered abnormal. Of fifty-seven patients with liver disease, 84.2 per cent had a reduction of serum albumin:

Neoplasm	.....	100.0 per cent
Hepatitis	.....	90.9 per cent
Cirrhosis	.....	80.5 per cent

The Takata-Ara test was included as a test of serum proteins since it is believed to depend upon the globulin fraction of the serum protein. It is not a specific test of liver function but frequently is positive in widespread hepatitis. In fifty-six patients, the authors found the test positive in 51.8 per cent:

Hepatitis	.....	66.7 per cent
Neoplasm	.....	50.0 per cent
Cirrhosis	.....	48.8 per cent

No definite relationship was found between this test and serum protein levels or albumin/globulin ratios.

6. Bromsulfalein Test—In the absence of jaundice, this test was found to be of great value in indicating hepatic disease. Any direct or biphasic Van den Bergh reaction indicates some biliary obstruction and renders the test valueless. The authors used 5 mg. of dye per kilogram of body weight and tested retention in the blood at thirty minutes. Retentions of 15 per cent or more was considered abnormal. Of twenty-nine patients with liver disease with indirect Van den Bergh reactions, twenty-five (86.2 per cent) showed positive dye retention:

Hepatitis .....	100 per cent
Neoplasm .....	100 per cent
Cirrhosis .....	84 per cent

7. Macrocytosis—In fifty-eight cases of liver disease, mean corpuscular volume determinations were made. The greatest incidence of macrocytosis was found in cases of cirrhosis:

Cirrhosis .....	63.4 per cent
Hepatitis .....	45.5 per cent
Neoplasm .....	16.6 per cent

The authors concluded that in the presence of jaundice the best tests for the estimation of liver function are the serum protein determination and the glucose tolerance test. In the absence of jaundice, the best tests are the urinary urobilinogen test and the bromsulfalein dye excretion test. The Van den Bergh test should be done in all suspected cases. Repetition of these tests from time to time during the disease will give evidence of progression, regression, or a stationary course.

MULTIPLE TESTS ON SINGLE BLOOD SAMPLE—In an effort to simplify the testing of liver function, Schwimmer *et al.*<sup>28</sup> selected a group of tests, all of

which can be done on a single 12-cc. blood sample. The tests included: (1) Icterus index; (2) Van den Bergh reaction; (3) cephalin-cholesterol flocculation; (4) serum phosphatase (alkaline); (5) total cholesterol and cholesterol esters; (6) total serum proteins and albumin-globulin ratio.

Over 1400 of these composite tests were done on 750 patients. It was found that the cholesterol ester/total cholesterol ratio and the cephalin flocculation reaction were the most sensitive indices of intrahepatic disturbance, the percentage of esters being the more reliable of the two. With severe hepatic damage, both tests have given unequivocally positive results. In lesser degrees of hepatic damage (early hepatocellular jaundice, cirrhosis, chronic passive congestion), a positive cephalin flocculation test usually precedes a reduction in cholesterol esters. In progressive obstructive icterus with beginning hepatic involvement, lowered cholesterol ester ratios were commonly found while cephalin flocculation was still negative. Of least diagnostic value were the blood protein tests, but A and G values and A/G ratios were of some value in prognosis and in evaluating results of therapy. There was no relationship between protein studies and other function tests.

Icterus index, phosphatase, and total cholesterol levels were correlated in early obstructive jaundice, but in subsiding icterus the icterus index fell more rapidly than the other two. As liver damage appeared in prolonged obstruction, the phosphatase and cholesterol fell while the icterus index remained elevated. In these instances, too, an immediate or delayed Van den Bergh reaction usually changed to a biphasic one.

CEPHALIN-CHOLESTEROL FLOCCULATION TEST—In an effort to evaluate this test, Wade and Richman<sup>29</sup> studied 178

patients with parenchymatous liver disease. Positive flocculation tests were obtained in 173. Of 45 patients with discrete hepatic lesions involving only a small amount of parenchyma, only 24 showed significant flocculation. Positive tests were obtained in 67 cases in a series of 180 who had suggestive evidence of hepatic disease; of these positives, 21 had cholecystitis and cholelithiasis, 24 had chronic passive congestion, and 8 were chronic alcoholics. In 105 controls, 19 gave positive tests, 12 of whom showed evidence of active infection. False positives were also obtained in some cases of allergy and during the puerperium or neonatal period.

In comparison with other liver function tests, the authors concluded that the cephalin-cholesterol flocculation test was superior in detecting diffuse hepatic disease. Intravenous hippuric acid and bromsulfalein gave more frequent indication of hepatic disease in the presence of discrete or focal lesions of the liver. The flocculation test proved of no value in the differentiation of obstructive and nonobstructive jaundice.

**HIPPURIC ACID EXCRETION**—Further observations on the value of the hippuric acid liver function test were reported by Page and Preisler.<sup>30</sup> It was their aim to determine whether: (1) Repeated tests on the same patient might reveal to what extent this detoxifying function of the liver changes during the course of the disease; (2) tests performed early in the disease might be of prognostic value, and (3) the liver function as measured by this test later returns to normal.

Sixty young male adults with acute infective hepatitis received repeated intravenous hippuric acid tests. Control studies were done on ninety patients without evidence of liver disease.

Procedure: (1) Nothing allowed by mouth after 9 P. M., the day before the

test; (2) patient voided at 6 P. M. and the specimen was discarded; he then drank two glasses of water; (3) two hours later the bladder was emptied and 1.77 gm. of sodium benzoate in 20 cc. of distilled water was injected intravenously over a period of five to eight minutes; (4) the patient then drank two glasses of water and one hour later the bladder was completely emptied and the urine analyzed for hippuric acid.

*Technic of Urine Determination*—The entire one-hour specimen of urine was adjusted to a volume of 100 cc. with water after evaporating to below this amount, then filtered. To the filtrate was added 50 gr. of ammonium sulfate and 5 cc. of concentrated hydrochloric acid and, when necessary, a small quantity of hippuric acid to induce crystallization. After standing at least an hour, the crystals were filtered off on a weighed Gooch crucible fitted with filter paper, washed with four 5 cc. portions (20 cc.) of dilute hydrochloric acid (5 cc. of concentrated acid per 100 cc.), dried at 110° and weighed. A correction factor (amounting to 0.15 gm. for the conditions used) for the amount of hippuric acid not recovered because of solubility, retention in filter paper, washing, and residual amounts left in the vessels, was determined by treating known amounts of hippuric acid through the complete procedure.

The per cent of normal excretion was determined by dividing the actual excretion of hippuric acid in grams by the estimated normal excretion in grams. Estimated normal excretion was calculated by the formula: Hippuric acid =  $0.34 + (0.00668 \text{ times body weight in pounds})$ .

During the first five days of illness, all the acute hepatitis cases showed hippuric acid secretion below 95 per cent of normal, the mean being 61 per cent. The excretion rose during the next nine days with a mean of 78 per cent. When the initial excretion was below 50 per cent of normal (nine patients), it took an average of ninety days for excretion to return to normal. When an initial excretion was between 51 and 70 per cent of normal, the average time for return to normal was twenty-eight days.

The mean hippuric acid excretion of the control group (90 patients) was 102.7 per cent plus/minus 7.3 per cent. The authors concluded that the hippuric acid excretion is markedly diminished during the first five days of clinical jaundice in acute hepatitis. After this initial low excretion, the subsequent levels rise rapidly as recovery occurs. The prognostic value of the test is indicated by the relationship between low excretion of hippuric acid and long convalescence as compared with shorter recovery periods in patients with higher levels of hippuric acid excretion.

**PROTHROMBIN RESPONSE TO VITAMIN K IN LIVER DISEASE**—As a result of experimental work on dogs, in which liver damage was induced by injection of carbon tetrachloride, Shapiro and Richards<sup>31</sup> concluded that determination of prothrombin time offered a reliable index of the severity of hepatic damage. Prolongation of prothrombin time ran roughly parallel with bromsulfalein dye retention. Administration of synthetic vitamin K to several of the dogs did not change the rate of recovery in these experimental animals.

Since prothrombinopenia had been reported by others in human hepatic disease, the authors studied a series of twenty-three cases using a special dilution technic for determining plasma prothrombin time and observing the response to large doses of synthetic vitamin K (hykinone). Included in the series were eighteen cases of Laënnec's cirrhosis, two of hemochromatosis, and cases of acute arsenical hepatitis, metastatic neoplasm, and macrocytic anemia. Of twenty-three cases, only three showed normal prothrombin levels. Twenty had moderate or marked prolongation of prothrombin time (one and one-half to two times normal).

After daily administration of synthetic vitamin K for several days to cases of prothrombinopenia, three types of response were noted: (1) An initial reduction of prothrombin time toward normal for one to three days when it became prolonged, then gradually fell to the original level; (2) the prothrombin time remained at about the original level for two to three days when it became increased for two to three days and gradually receded to or slightly below the original; (3) where the resting level of prothrombin was normal, after the third or fourth day of vitamin K medication, the prothrombin time increased slightly, at which figure it remained for a few days, then returned to normal. This latter was interpreted as indicating an exhaustion of the prothrombin mechanism.

The authors concluded that in the presence of liver disease, an established prothrombinopenia cannot be restored to normal by the administration of synthetic vitamin K. Such a sequence of changes portends liver disturbance (unless other explanations are discovered). In four of the reported cases, liver disease was indicated by the prothrombin determinations in which the bromsulfalein test had been negative.

**VITAMIN A IN JAUNDICE**—Ruffin and Wise<sup>32</sup> determined plasma vitamin A levels in two groups of patients: Those with diffuse liver damage or acute hepatitis, and those with common duct obstruction. The lower limit of normal for vitamin A was taken as 75 I.U. per cent and for carotene, 164 I.U. per cent. Determinations were made on 100 normal controls, 10 cases of obstructive jaundice, and 17 cases of acute hepatitis.

In every case of acute hepatitis, the vitamin A was significantly lowered with levels from 20 to 60 I.U. per cent during the acute stage followed by a grad-

ual increase to normal during recovery. Carotene levels were not significantly altered. There was no constant correlation between vitamin A levels and other tests of liver function except the cephalin flocculation test, which was positive in every case. In ten cases of operatively proved obstructive jaundice, six showed no evidence of hepatic involvement and the vitamin A levels were close to normal limits. In four patients, the levels were definitely lowered, but in each case either the duration of the disease or obvious infection were factors which could have resulted in liver damage.

**EFFECTS OF NEWER DRUGS ON THE LIVER—Thiouracil**—In a series of forty-three patients with toxic goiter treated with thiouracil, Gargill and Lesser<sup>33</sup> reported two cases of jaundice. This complication appeared during the second or third week of drug administration. In one instance, the icterus persisted for 100 days and in the other for 26 days. Clinically, these patients resembled those suffering from postarsphenamine jaundice; however, pruritus was a prominent feature in each and in one instance a liver biopsy showed no evidence of parenchymal hepatic damage. The microscopic section showed "prominent central veins and normal parenchymal cells. The sinusoids were clearly demarcated and empty, well lined with prominent Kupffer cells. The bile capillaries between the cells of the liver cords were manifestly distended. Those in the outer half of the lobule were distended but empty, while those in the inner half of the lobule were distended and plugged with yellow-green bile pigment. In the portal areas, the larger bile ducts were empty but showed evidence of recent distention by the prominence of their open lumens. The portal areas were infiltrated with some mononuclear and rare

polymorphonuclear cells. The histologic picture described is that usually associated with acute bile stasis." The gallbladder, cystic and common bile ducts were normal. Blood counts were not included in the report. Liver function tests were negative for evidence of parenchymal disease.

**Atabrine**—Because of the common belief that the skin discoloration in persons taking atabrine for the suppression or active therapy of malaria was due to actual jaundice secondary to liver damage, Butt *et al.*<sup>34</sup> studied fifty patients who were given large doses of this drug (4.5 gm. in ten days). A series of tests was done before and after the administration. These included: (1) Bromsulfalein dye test; (2) prothrombin time; (3) serum bilirubin; (4) Van den Bergh; (5) blood count, and (6) smear for malaria.

In spite of repeated attacks of malaria suffered by most of these subjects, only two showed bromsulfalein dye retention and these between 6 and 12 per cent in one hour, one before starting the drug, and the other at the completion of the test. The other tests used were persistently negative throughout except for a change in the Van den Bergh reaction from indirect to direct or *vice versa*, which did not seem to be significant. It was concluded that even in relatively large doses there was no evidence of significant hepatotoxic action of atabrine.

**Amebic Hepatitis**—A series of thirty-three patients with amebic hepatitis was reported by Soderman and Lewis.<sup>35</sup> These writers warned that amebic hepatitis was not to be confused with frank abscess formation which they prefer to call hepatic amebiasis.

**Symptoms**—Pain in the liver area was a universal complaint and varied from sharp and severe to dull and aching.



Fever was present in all but one case. Jaundice appeared in five cases. Nausea, vomiting, and weakness were frequent complaints. Diarrhea was present at onset or during the course in only 27 per cent of this series, although several others gave a history of diarrhea, giving a total incidence of diarrhea up to 48.5 per cent.

Physical examination revealed hepatomegaly and tenderness in the hepatic area in 88 and 100 per cent respectively. The leukocyte count was elevated (average 13,000) in 88 per cent. Stools revealed *E. histolytica* in 54.5 per cent of this series. X-ray evidence of hepatic involvement (diaphragmatic elevation and fixation) was present in 45.4 per cent of this group as compared with 81 per cent in patients with frank hepatic abscess.

Treatment advised consisted of emetine hydrochloride 0.06 gm. (1 grain) intramuscularly daily for six to ten days followed by diodoquin, three tablets of 0.2 gm. (3.2 grains) three times daily for five days. The authors advise this course of therapy on a strong suspicion of amebic hepatitis since if the disease is allowed to progress, abscess formation is likely with an increasing mortality rate. In the authors' experience, the mortality in amebic hepatitis is nil, while in amebic abscess it is 5.2 per cent. Use of treatment without careful diagnostic studies is advised against, however.

### Colon

**Amebic Colitis** — The problem of amebiasis was reviewed by Silverman and Leslie.<sup>36</sup> The authors stated: "Amebiasis is far more prevalent in the United States than is generally appreciated. Although areas of hyperendemicity, such as are present in the Orient and tropics, are not found in this country, the states bordering the Gulf of Mexico may be

generally considered as comprising an endemic area, and sporadic cases have been observed over the entire country. In New Orleans alone, it has been estimated that the protozoon is harbored by close to 15 per cent of the general population. Most of these cases are symptomatically below the clinical threshold. Amebic colitis exists as a pathologic entity without the classic picture of dysentery in a high percentage of the cases. . . . The symptomatology varies from mild, rare, abdominal discomfort and constipation to acute abdominal pain of the most extreme degree and uncontrollable diarrhea; the duration may range from a few days to many years. The disease often simulates other abdominal conditions so closely that patients undergo laparotomy for such presumptive diagnoses as chronic cholecystitis, appendicitis, pancreatitis, and intestinal obstruction. . . . The pathologic picture varies from patient to patient and may vary in the same patient at different times from a few widely separated, slightly undermined ulcers to a sloughing, necrotizing, serpiginous generalized ulceration of the entire colon. Furthermore, granulomatous tumors of amebic origin may be encountered anywhere in the large intestine."

The authors presented three cases of the "ulceronecrotic" form of amebiasis characterized by the formation of granulomatous lesions with necrosis of large sections of the colon. In two of these cases, postmortem examination revealed ameba in all layers of the colon; in the third case, no amebae were found. The cause of such a severe form of the disease is not apparent. "As Faust pointed out, cases with acute fulminating symptoms commonly occur in outlanders becoming infected in hyperendemic areas, where among the natives the incidence of the infection is high and the inci-

dence of clinical symptoms low. Cases of chronic nature, on the other hand, may be seen anywhere, as are cases manifesting acute exacerbations of the chronic state."

**Treatment of Chronic Amebic Dysentery**—Hargreaves<sup>37</sup> presented a patient who was seriously ill with chronic amebic dysentery and who had been treated repeatedly by standard measures without success. The stools continued to show blood and amebae. He was given an initial dose of 100,000 units of *penicillin* intramuscularly followed by 33,000 units every three hours until over a million units were given. In twenty-four hours he was free of pain and fever and in forty-eight hours he passed a formed stool for the first time in two years. Amebae persisted in the feces, however, and after two weeks there was a recurrence of bloody diarrhea. A second course of two and one-quarter million units of penicillin resulted in remission but amebae persisted. *Emetine bismuth iodide* by mouth eventually cleared up the amebiasis.

Forty-seven cases of severe, refractory amebiasis were treated along similar lines. In some the penicillin was not effective and *succinyl sulfathiazole* was given concurrently by mouth (total 80 gm.). In only a few cases was more than one course of emetine bismuth iodide required to cure the amebiasis after such treatment.

**Toxicity of Amebicides**—Although many cases of successful therapy with *diodoquin* have been reported without toxic effect of the drug, some dangers in its use exist, according to Silverman and Leslie.<sup>38</sup> These writers presented three cases which showed toxic manifestations in the form of furunculosis in two and a diffuse toxic erythema in the third. It was thought that these reactions were due to unusual absorption

or sensitivity to the iodine contained in the drug. The authors concluded that in view of the large number of patients treated with this preparation, the incidence of untoward symptoms is low and does not negate the therapeutic efficacy of diodoquin.

The possible dangers of promiscuous use of *diodoquin* and other amebicides was stressed by David.<sup>39</sup> Experimental studies showed that appreciable amounts of iodine were absorbed by animals and humans given diodoquin. Some of the patients complained of pruritus ani, gastric discomfort, and skin warmth. Similar results were obtained with *vioform* and *chiniofon*. Elevation of blood iodine was demonstrated during treatment. The author recommended certain definite rules for the administration of amebicides: "(1) Treatment should be limited to a short period of from ten to fourteen days; (2) a rest period of at least two or three weeks should be followed and the stools found positive for the amebae before another course of treatment with one of the oral amebicides is started; (3) the iodine-containing compounds chiniofon, vioform, and diodoquin, and the arsenicals, carbarsone and acetarsone, are contraindicated in patients showing or suspected of having liver damage or known to have drug sensitivity; (4) none of these drugs should be used empirically for the treatment of a nonamebic diarrhea; (5) *emetine hydrochloride* should not be used in weakened individuals or those with heart damage, because this drug has a definite toxic action on the heart and neuromuscular system."

**Bacillary Dysentery**—The effectiveness of *bacteriophage* in the treatment of bacillary dysentery was studied by Morton and Engley.<sup>40</sup> After a careful review of the literature, these authors stated that "the reports on the therapeutic

tic trials of dysentery phage in man are inconclusive. This is in part due to the nature of the experiments, and the problem of the therapeutic action of dysentery phage must be considered as still unsettled." "In experimentally induced infections with dysentery bacilli in laboratory animals, dysentery phage has demonstrated an unmistakably therapeutic action." "Prophylactically, it has been shown that dysentery phage is capable of preventing bacillary dysentery in man and also capable of preventing lethal infections experimentally induced in laboratory animals." It was suggested that "the next phase in the history of dysentery phage should be carefully planned prophylactic and therapeutic trials on human beings, taking advantage of the knowledge gained from *in vitro* tests and *in vivo* tests in experimental animals. Quite illogically, tests on man were made before the dysentery phage was tried on experimental animals."

**Sulfonamide therapy** was reviewed by Felson.<sup>41</sup> Best results were obtained by combining a relatively nonabsorbable with a freely absorbable sulfonamide, such as sulfadiazine or sulfathiazole and sulfasuxidine. The following dosage was recommended: Sulfadiazine or thiazole, 4 gm. in first four hours, then 1 gm. every four hours with a similar dose of sulfasuxidine. The program of treatment was as follows:

1. Dosage—0.25 gm. per kilogram.
2. Earlier medication started, better the results.
3. Continue medication for at least three days after symptoms and signs have subsided.
4. Discontinue drug immediately renal or toxic manifestations.
5. Check healing by direct sigmoidoscopy.
6. Check infectivity by cultures on tenth, twelfth, and fourteenth days of disease; then weekly for one month.

**Ulcerative Colitis**—*Treatment with intestinal mucosal preparations* was

suggested by Gill.<sup>42</sup> Because the natural history of many cases of "idiopathic" ulcerative colitis is characterized by spontaneous remissions and relapses, this writer considered the possible importance of some type of deficiency. Preliminary studies suggested that the hypothetical factor might be present in or produced by the intestine itself. Feeding experiments in one case over several years showed that remissions could be induced regularly by giving uncooked pig's small intestine by mouth. Relapses followed discontinuance of this therapy. In several other cases, good results were obtained, but in others there was little benefit. A preparation of pig's small intestinal mucosa, dried and defatted and given by mouth as a powder, also produced some remissions. Parenterally administered extracts have been without effect. The author concluded that in some cases of ulcerative colitis, a deficiency factor is of importance and may be overcome by an extract of pig's intestine.

**Sulfonamides**—The use of sulfathalidine (phthalylsulfathiazole) in patients with infectious and ulcerative lesions of the colon was reported by Streicher.<sup>43</sup> In a series of 100 cases there were 80 cases of ulcerative colitis, 6 of amebic dysentery, 2 of bacillary dysentery, 2 with paratyphoid, and 2 with *Dientameba fragilis*. In the patients with ulcerative colitis, good response was obtained in both acute and chronic cases. Improvement was noted within seventy-two hours with a decrease in cramps, less diarrhea, and increased formation of the stools. In acute cases, the temperature was rapidly controlled. After clinical observations, the author concluded that the optimal dose of the drug was 3 gm. daily. No toxic effects were noted following prolonged medication, and with doses as high as 12 gm. daily,

the only deleterious effect was an increase in abdominal cramps and diarrhea. Blood studies showed levels of from 0.5 to 1.5 mg. per cent regardless of the daily dose. Fecal studies revealed that 55 to 65 per cent of the drug was recovered in the stools on a 3 gm. daily dose. Urine excretion accounted for about 5 per cent of the oral dose. Bacteriologic studies on the feces demonstrated a reduction of *Escherichia coli*, streptococci, staphylococci, and total bacteria. This effect was noted more quickly with large doses of the drug, but similar levels were reached after one week with the 3-gm. dose.

The effectiveness of other sulfonamides in ulcerative colitis was reviewed in a symposium in Gastroenterology, January, 1945. According to Pollard,<sup>45</sup> succinyl sulfathiazole (sulfasuxidine) produced a definite and at times dramatic response in three fourths of thirty-six patients studied. Few toxic effects were noted. Collins<sup>46</sup> reported that "after seven years' experience, the use of various sulfonamides has not proved so encouraging as the initial experience led us to expect. The use of sulfonamides has not proved so helpful in ulcerative colitis as in other inflammatory conditions. At the same time, many of our patients attributed their return to a useful life to this form of therapy." "We believe sulfonamides have a place in the treatment of ulcerative colitis, but we do not know which patient will be benefited. At the present time we routinely give each patient at least a short trial on sulfonamide therapy, not as a specific remedy, but as an adjunct to the usual treatment of rest, elimination of vitamin and mineral deficiencies, and the administration of blood transfusion and parenteral fluids in severely toxic cases."

**Penicillin** has not been reported to exert any favorable effect on cases of

chronic ulcerative colitis in the hands of most investigators.

**Congenital Megacolon**—The effectiveness of left lumbar sympathectomy in the treatment of congenital megacolon was reported by Penick.<sup>44</sup> Of eleven cases so treated, satisfactory results were obtained in ten. According to this writer, successful surgery depends upon careful selection of cases. Before operation was attempted, the reported cases had been shown to have persistent dilatation of the colon by barium enema studies. A course of medical treatment, using *mecholyll bromide* and/or *antispasmodic drugs*, was tried. A therapeutic test of spinal anesthesia may be a deciding factor in choosing sympathectomy in preference to colonic resection, since in the experience of this author, sympathectomy is not likely to give satisfactory results if spinal anesthesia fails to produce bowel evacuation and decreased volume of barium required to fill the colon. In none of the reported cases was there any operative complication. Seven were classified as being highly satisfactory, three greatly improved, and one failure. The ages varied from one and one-half years to fifty-two years.

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## HEMATOLOGY

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### The Spleen

In its normal state, the spleen is a relatively small organ of about 50 to 100 gm., containing a variable amount of blood. Its "reservoir" function was thoroughly studied years ago by Bancroft (1925). Removal of the normal spleen is followed by a number of interesting blood changes (1941): A tendency to increase in the red cell count, the development of thin red cells (target cells) with increased hypotonic *resistance*, and the development of Howell-Jolly bodies (nuclear remains) in the red cells; an increase in the leukocyte count; an increase in the platelet count. These changes indicate a definite relationship

between the spleen and the blood-forming organs, notably the bone marrow, perhaps mediated by splenic hormones. The presence of red cells with nuclear fragments in the blood might indicate a splenic influence on denucleation of the red cell. Leukocytosis and thrombocytosis might be indicative of spleen-granulocyte and spleen-megakaryocyte relationships. The development of thin red cells after splenectomy probably indicates that the mature red cells become thicker in the numerous passages (and sojourns?) through the splenic sinusoids. Although it is reasonable to assume that the spleen makes red cells thicker, and thus prepares them for eventual breakdown as

they become more and more spherocytic, it is not definitely known that the spleen actually destroys red cells. The old saying that the spleen is the "graveyard" of the red cells may have to become modified. Singer and Weisz,<sup>1</sup> by studying the bile excretion of normal and splenectomized dogs after phenylhydrazine hemolysis, demonstrated that there was no decrease in bile pigment output in the splenectomized animals. Thus, in dogs at least and under the conditions of these experiments, it would seem that the spleen had little, if any, influence on blood destruction. These results, so contrary to our long accepted thoughts on this subject, must be confirmed in other animals and by different experimental methods before they can become completely accepted. The life span of the erythrocyte, as determined in these experiments, was approximately 110 days, and thus in line with the more recent investigations on this point. Thus, it would seem that less than 1 per cent of the red cells are destroyed daily. The actual methods of red cell destruction in the normal animal are but little known, and may simply be a matter of increased spherocytosis and gradual wearing down (fragmentation?).

**The Spleen as an Endocrine Organ; Hypersplenism**—The spleen is not ordinarily included among the organs of internal secretion, but it would seem that more and more evidence, to be sure, largely of the indirect type, is piling up to indicate that the spleen produces hormones which enter the blood stream and have effects on remote organs, notably the bone marrow. The recent series of observations of White and Dougherty<sup>2</sup> indicate a hormonal relationship between the adrenad cortex and lymphoid tissue. Ungar<sup>3</sup> has recently isolated from the normal spleen of guinea-pigs a crystalline substance which he calls "splenin," and which has the property of causing a

reduction in the bleeding time, an increase in the capillary resistance, and an inhibition in the release of histamine from blood cells. It was found that the spleen participated in the endocrine response to tissue injury and played a part in the control of protein metabolism. These results, although they require amplification and confirmation, are among the first clear cut and direct bits of evidence of the presence of splenic hormones. The relationship of so-called "splenin" to "thrombocytopen," described a number of years ago by Troland and Lee (1938), remains to be determined. It would appear both from clinical studies and from the study of extracts of spleens removed in idiopathic thrombocytopenic purpura, that the spleen in this disease contains a material (hormone?) which has distant effects on the production of platelets from the megakaryocytes of the bone marrow. Since the platelet count becomes and remains very high following splenectomy in the normal animal and individual, and since splenectomy in idiopathic thrombocytopenic purpura is followed by a dramatic increase in platelets, it seems reasonable to conclude that the spleen in that disease contains an excess of the normal platelet-regulating substance. Idiopathic thrombocytopenic purpura might therefore be a form of "hypersplenism." Confirmatory, in a clinical way, of this concept is the frequent presence of thrombocytopenia in patients with splenomegaly, and the return of the platelets to normal or above normal following splenectomy. The results with the injection of splenic extracts from cases of idiopathic thrombocytopenic purpura have been inconsistent, about one half the investigators having confirmed Troland and Lee's original observations, and about one half reporting no platelet reduction. Recent experiments in our laboratory,<sup>4</sup> using

dogs as the test animal, indicate the presence of active megakaryocyte-platelet inhibitor in splenic extracts from cases of the disease.

*Hypersplenism:* The spleen normally exerts very definite effects on the bone marrow, causing both quantitative and qualitative changes in the blood cells. These normal effects, although quite definite, seem to have but little importance since the splenectomized individual can live a healthy normal life without shortening of the life span. It is under pathologic conditions, however, that the spleen may develop unusual importance and may even be detrimental to life. When the splenic physiology becomes abnormal, various effects may ensue, connected with the bone marrow and blood. The bone marrow produces three types of cells: Red, granulocytes, and platelets, and splenic or "hypersplenic" effects (that one can determine) are anemia, neutropenia, thrombocytopenia, or various combinations of these. Hypersplenism may thus be "selective" or "total." If total, "pancytopenia" is present.

Splenic thrombocytopenia is the best known of the forms of hypersplenism. Idiopathic thrombopenic purpura occurs suddenly in many cases and is prolonged, with remissions and relapses, in others. Recent studies of the bone marrow by Dameshek and Miller<sup>5</sup> show that platelet formation by the megakaryocytes of the bone marrow is greatly reduced, but that following splenectomy, platelet formation becomes enormously increased, leading to a quick increase in the platelets in the blood. It appears that an active material is present in the spleen of this disease, causing inhibition of growth and delivery of platelets from the bone marrow megakaryocytes to the blood. Thrombocytopenia may be "primary" or idiopathic, or it may be "symptomatic" of many conditions causing

splenomegaly. Thus in portal hypertension (cirrhosis of the liver, etc.), in disorders of fat metabolism (Gaucher's disease), in chronic infectious splenomegaly, etc., the platelet count often becomes reduced, at times greatly so.

Splenic anemia has been talked about for years, but has been largely discarded as a term in modern writings, because it became a term covering many different disorders in which two features were present: Anemia and splenomegaly. Many cases of leukemia, Cooley's anemia, sickle cell anemia, etc., were called "splenic anemia," until finally one investigator after another pulled out from this wastebasket a different and highly specific disease. This left very little that might be called splenic anemia.

Abrami,<sup>6</sup> in a recent number of the French hematologic journal, "Le Sang," comes out for revival of the term to include cases in which there is splenomegaly and anemia and in which splenectomy is therapeutically successful. Many cases of hemolytic anemia are cured by splenectomy. In some of these, the red cells are defective; in a few, usually when the leukocyte and platelet counts are also reduced, the spleen seems to be at the central point of the disease picture and splenectomy is dramatically successful. These cases are probably examples of hypersplenism with splenic anemia. Whether the spleen exerts chiefly a hemolytic effect in these cases or whether it also has an effect on maturation of red cells or their delivery from the bone marrow to the blood is not as yet completely clear.

Splenic neutropenia is gradually becoming better known as a definite syndrome. This condition seems to be a form of *hypersplenism* in which the bone marrow granulocytes are chiefly affected. First described by Frank in 1916 under the term of "aleukia sple-

nica," the syndrome was revived more recently by Wiseman and Doan (1942) under the designation of splenic neutropenia. Briefly, the combination of leukopenia, extreme granulocytopenia, and splenomegaly is present. Frequent pyogenic infections and fever are commonly present. Studies of the bone marrow rule out the presence of leukemia, lymphosarcoma, etc., and show increased numbers of granulocytes, despite the low granulocyte count in the blood. If the various studies and interpretations have been correct, splenectomy is followed by a quick return in the granulocyte-leukocyte levels to normal or better than normal levels. Splenic neutropenia may be completely idiopathic, *i. e.*, the cause of the splenomegaly may be quite obscure, or it may be associated with the splenomegaly of certain cases of rheumatoid arthritis (Felty's syndrome), Boeck's sarcoid, Gaucher's disease, tuberculosis of the spleen, malaria, kala-azar. In any of these (and other conditions with splenomegaly) the neutropenia may become so severe as to lead to recurrent bouts of infection and fever. Patients with this syndrome often go about from clinic to clinic without definite diagnosis, their lives frequently in jeopardy on account of the frequent development of pyogenic infection. Splenectomy has been dramatically successful in an increased number of cases. Recent reports include those of Langston, White, and Ashley,<sup>7</sup> Rogers and Hall,<sup>8</sup> and Salzer, Ransohoff, and Blatt.<sup>9</sup>

Splenic "pancytopenia" or "panhematopenia" (the latter term has recently been used by Doan and Wright<sup>10</sup>) includes cases with splenomegaly in which there is a simultaneous reduction in all the cellular elements of the blood. Many cases of splenic neutropenia have more or less marked thrombocytopenia and/or anemia; the neutropenia is simply out-

standing. It is of great importance to recognize in these cases that the pancytopenia is not due to aplasia or hypoplasia of the marrow, but is brought about by an inhibitory effect (Doan thinks a phagocytic effect is responsible) of the enlarged spleen on the bone marrow. Many of these cases go about for years unrecognized because either the spleen is not felt or the pancytopenia suggests the presence of a hypocellular marrow. Sternal marrow studies reveal hypercellularity of all the elements with large numbers of nucleated red cells, granulocytes, and megakaryocytes. If the diagnosis and interpretations of the marrow picture are correct, splenectomy is dramatically successful.

These views, although relatively new, are being rapidly bolstered by increasing numbers of clinical cases. Together with other bits of evidence, chiefly from pathologic material, they strongly indicate the presence of splenic hormones having at times deleterious effects on the maturation and delivery of cells from the bone marrow to the blood. There is need for more direct evidence bearing upon these points.

**Rupture of the Spleen**—With enlargement of the spleen in certain infectious states, notably in malaria and infectious mononucleosis, spontaneous rupture may occur, giving the symptoms of hemorrhage, shock, and abdominal emergency. Russ and Gaynor<sup>11</sup> report the case of a soldier who had had a single attack of vivax malaria overseas. Eleven months later, in this country, he developed a malarial chill which was accompanied by acute pain in the left shoulder radiating and localizing in the left upper quadrant of the abdomen. Operation revealed a ruptured spleen with the abdomen filled with both fresh and old blood. Splenectomy was followed by recovery, but nine days post-



operatively another chill occurred and the plasmodium vivax was recovered. Another case, also in a returned soldier, is reported by Kellner, Hochstein, and Tillman.<sup>12</sup> In this case, shock quickly developed and, before operation could be performed, the patient died. At post-mortem examination, the abdomen contained 2500 cc. of fresh blood. The spleen was very soft and presented a transverse laceration in its midportion, together with several other small stellate lacerations. It is suggested that great caution be observed in palpating for the spleen in an acute attack of malaria.

Although infectious mononucleosis is almost always a benign disease, subject to but few complications, it is occasionally accompanied with serious symptoms. In one case seen with Dr. Grossi, of Haverhill, severe thrombocytopenic purpura developed, requiring splenectomy. Reports of splenic rupture are increasing in number. Davis, MacFee, Wright, and Allyn<sup>13</sup> report a typical case of the disease in a young man who was suddenly seized with sharp pain in the left upper quadrant of the abdomen, pain in the left shoulder, and the symptoms of shock. At operation, a wide longitudinal split of the splenic capsule was found, together with two tears in the pulp. The splenic pathology was typical of infectious mononucleosis. Recovery ensued. Other cases have been described by King (1941), Darley, Black, Smith, and Good,<sup>14</sup> Ziegler,<sup>15</sup> and by Vaughan, Regan, and Terplan.<sup>16</sup> Rupture in the latter case took place with simple straining at stool.

Splenic rupture associated with aneurysm of the splenic artery is reported by Martin.<sup>17</sup> A naval officer, aged 36, suddenly developed pain in the left upper quadrant of the abdomen, which was quickly followed by shock and death. At autopsy, a perforated aneurysm of

the splenic artery just proximal to the gastropiploic branch was found. The abdomen was filled with blood. No clue as to the etiology of the aneurysm was discovered and the remainder of the vascular system was normal. It should be noted that the splenic arterial system is often sclerosed and tortuous out of all proportion to the remainder of the vascular tree. Malformations of blood vessels are common.

Splenic rupture occurring spontaneously in an apparently normal spleen is reported by Duby.<sup>18</sup> A twenty-eight-year-old married woman was suddenly seized with severe upper abdominal pain, difficult breathing, and fainting. It was thought she might have an ectopic pregnancy with rupture, and operation was performed. Large amounts of intra-abdominal blood were found and at exploration an enlarged, soft spleen was discovered with a large rent near the upper pole. Splenectomy was followed by recovery. The spleen weighed 340 gm. and showed multiple lacerations. No cause for the rupture was obvious and the splenic histology was unrevealing.

**Tumors, Cysts, Accessory Spleens, etc.**—Bostwick<sup>19</sup> reviews the cases of primary neoplasms of the spleen, 157, in the literature, adding 7 of his own. Seven types are discriminated: Angioma (either hemangioma or lymphangioma), lymphoma, reticuloendothelial neoplasm, embryonic inclusions including various types of cysts, fibrosarcoma, leiomyosarcoma, and neurosarcoma. A report from Argentina by Unchalo, Mainetti, and Cuculicchio<sup>20</sup> relates an interesting case of a young woman with fever, cough, weight loss, and an enlarged spleen who showed the hooks of *Taenia echinococcus* in the sputum. At operation, a large cyst was found replacing the spleen. Formalization and marsupialization were per-

formed without splenectomy. Almost three years later, another abdominal operation was required and an exploration disclosed complete absence of spleen in the left hypochondrium with a thick irregular process adherent to the diaphragm and the tail of the pancreas. There had been no recurrence of the hydatid cyst. Another interesting case report of a splenic cyst is that of Jameson and Smith,<sup>21</sup> who described a calcified cyst in a student aged eighteen, who complained of left upper abdominal pain and whose x-rays showed a partially calcified mass in the left upper quadrant, not connected with the stomach or the kidneys. At operation, an enlarged spleen was found which was replaced in large part by a calcified cyst. Splenic cysts are rare, only 152 of all types having been reported to 1941; calcification has been reported only 7 times. In a case personally observed, a large mass in the upper abdomen and left upper quadrant was thought to be of splenic origin because the leukocyte count was low and contraction occurred following the injection of adrenalin. Operation disclosed a very large unilocular cyst which was removed *in toto* with complete recovery.

Accessory spleens may be a very annoying feature, particularly in idiopathic thrombocytopenia purpura, and hemolytic anemia, following splenectomy. Recurrences in such conditions may be due to the abnormal activity of such a spleniculus. Rhame<sup>22</sup> reports the case of a young man whose spleen had been removed six years previously for traumatic rupture, and who now required abdominal operation. Exploration revealed a tumor in the midjejunum under the serosa of the antimesenteric border of the bowel, impinging on the bowel lumen. Several similar smaller tumors

were found along the greater curvature of the stomach, the lower margin of the transverse colon, and in the greater omentum. Microscopically, all the specimens removed were hyperplastic hemolymph nodes, having the appearance of splenic tissue except for the trabeculae. It is considered that in the young, after splenectomy, splenic function may be restored through hypertrophy of hemolymph nodes and by accessory splenic tissue. An unusual location for an accessory spleen is described by Olken,<sup>23</sup> who found at autopsy in a fifty-six-year-old man, who died of a bleeding peptic ulcer, a tail of accessory splenic tissue which passed through the inguinal canal into the scrotum, where a bulb of splenic tissue was located.

**Splenectomy** — The indications for splenectomy are discussed in a series of letters in "Modern Medicine" (May, 1945). These letters were solicited by the journal in response to the abstract of an article by Carpenter published in the same journal in March, 1945.<sup>24</sup> Dame-shek lists the following indications: *Absolute*: Rupture of the spleen; idiopathic thrombocytopenic purpura, particularly if it is acute; familial hemolytic jaundice of the spherocytic variety, if one or more crises have occurred; acute or subacute hemolytic anemia, if a few transfusions have proved ineffective, and if various specific causes for the increased hemolysis have been ruled out; tumors and cysts of the spleen, if properly diagnosed. *Probable*: Certain cases of splenic neutropenia; certain cases of Mediterranean and sickle cell anemia with unusual degrees of hemolysis; certain cases of splenic disease with pancytopenia. *Possible*: Certain cases of chronic congestive splenomegaly, including cirrhosis of the liver, etc., particularly with leukopenia and thrombocyto-

penia. Doan, in the same symposium, lists the following indications: Congenital hemolytic icterus, thrombocytopenic purpura hemorrhagica in which the marrow shows increased megakaryocytes, primary splenic neutropenia, primary splenic panhematopenia, any other type of splenomegaly associated with anemia, leukopenia, and/or thrombocytopenia. Doan's criteria for splenectomy are based essentially on the laboratory studies centered in sternal marrow aspiration with supravital studies of the removed cells, and the adrenalin test for splenic contraction. The latter, Doan believes, gives a "biopsy," as it were, of the cells "sequestered" by the spleen. (Doan believes that the spleen "sequesters" cells in idiopathic thrombopenic purpura and splenic neutropenia, rather than causing inhibitory effects upon the bone marrow.)

Cooley, in the last article published before his recent death (October 13, 1945), described a new refractory hypochromic anemia, associated with elliptocytosis, unresponsive to liver and iron therapy, and present as a familial trait.<sup>25</sup> There was apparently no Mediterranean or Negro admixture and no evidence of increased hemolysis. Splenectomy in one case resulted in a slow steady improvement. Cooley suggests that there is a group of anemias in which a defective type of hemoglobin or red cell formation is present, and which exhibits the presence of a splenic influence on the bone marrow.

Pappenheimer, Thompson, Parker, and Smith<sup>26</sup> report three cases of a severe form of hypochromic anemia (? hemolytic) not responding to liver or iron, and in which splenectomy was performed. The first two cases died of progressive anemia after splenectomy, and the anemia was unchanged in the third case. Following splenectomy, all patients showed in the red cells small iron-staining coccoid

or bacilloid bodies, having a superficial resemblance to Bartonellalike parasites. It was concluded that the bodies were probably iron containing and analogous to the "siderocytes" previously described by Grüneberg (1941).

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## DISEASES OF THE KIDNEY

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and

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### Introduction

Although this year's review of the literature on diseases of the kidney reveals no startling advances, many substantial papers have appeared which reflect progress in the various phases of kidney disease. Articles on fundamental research work on the kidney have been comparatively few, but many have come from the clinical field.

The war has popularized some renal disorders, such as the sulfonamide kidney. Considerable attention has been given to another disorder, the crush syndrome and the renal lesion associated with it. Bywaters<sup>1</sup> has given an exceptionally good description of the condition. This syndrome is of great importance, not only to physicians in war zones, but also in everyday life since any crush injury may result in the same syndrome. Another derangement of the kidney, resulting in oliguria, anuria, and azotemia, has been recognized in conditions causing shock.<sup>2</sup> These and other subjects of more recent interest will be reviewed rather completely.

### Renal Function

Impairment of renal function in patients with essential hypertension was studied by Isberg and Barker.<sup>3</sup> Two hundred cases of essential hypertension were investigated by means of urinalysis, maximum concentration test, and urea clearance test. They found that repeated negative urinalyses are not sufficient evidence to assume that kidney function is normal, but the combination of normal maximum concentrating ability and normal urinalysis is a good clinical indication of normal renal function. The con-

centration test is more sensitive than the urea clearance in detecting early kidney damage. Thirty-three per cent of their series showed impaired concentrating ability in the presence of normal urea clearance values, while only 3 per cent demonstrated an adequate concentrating ability in the presence of subnormal urea clearance.

McGeorge<sup>4</sup> compared the renal function of sixty-two healthy subjects with normal blood pressure with that of seventy-five subjects with benign hypertension. In all respects these two groups were as nearly comparable as possible. Renal function was assessed by studying the concentrations of urea and chloride in the urine after ingestion of 15 gm. of urea. The following conclusions were drawn: (1) The average renal function did not differ significantly in young subjects, whether hypertensive or not; (2) with increasing age, the renal concentrating power declined. This was approximately three times as great in the elderly hypertensive group as in the elderly nonhypertensive group; (3) the degree of impairment usually occurring in benign hypertension is comparatively slight; no cases with severely impaired function were encountered; (4) even in elderly subjects with benign hypertension, the concentrating capacity of the kidneys may be within normal limits, but this probably represents a fall below the level which would have been obtained when the individual was younger; (5) there was no significant relationship between impaired concentrating capacity (in the absence of albuminuria) and the presence or absence

of symptoms, such as headache, dizzy attacks, or cerebral thrombosis, frequently associated with benign hypertension; (6) decline in renal function with advancing age can be demonstrated by urea or chloride percentages, but evidence indicates that the expression  $C$  plus  $U/2$  ( $C$  is per cent of chloride;  $U$  is maximal per cent of urea) provides a more accurate index of this decline in both hypertensive and nonhypertensive individuals.

Renal function tests employed by urologists frequently give inaccurate evidence of kidney efficiency and provide inadequate information of the renal reserve. Rather than being tests of renal function and renal reserve, they are likely to be simple indications of renal failure, since they may not be abnormal until 50 per cent or more of the kidney capacity has been lost. Accurate measurements of kidney function must be used if more refined renal surgery is to be done to conserve functioning renal tissue. With this in mind, Dean, Abels, and Taylor<sup>5</sup> have adopted, for routine clinical use, several recently devised renal function tests. By collecting specimens from each kidney with ureteral catheters, they obtain information as to the state of glomerular filtration, tubular secretion, and resorption, and the rate of blood flow through each kidney.

These rates, according to Klopp, Young, and Taylor,<sup>6</sup> are constant for a given individual who remains untreated or does not suffer from a progressive renal or vascular disease. However from their studies, they believe that the value of certain functions may be altered by an attempt to measure a second renal capacity simultaneously. Therefore, unless successive observations on the same subject are repeated under identical conditions, the determinations may be in error. They conclude that:

(1) High plasma concentrations of glucose may decrease the apparent renal blood flow as determined by the clearance of p-amino hippuric acid; (2) high plasma concentrations of glucose do not alter the glomerular filtration rate but may decrease the maximum ability of the tubules to secrete p-amino hippuric acid; (3) high plasma concentrations of p-amino hippuric acid may increase the apparent tubular resorption of glucose; (4) when the plasma concentrations of both glucose and p-amino are raised, increased values of apparent glomerular filtration are obtained; (5) simultaneous measurement of more than one renal function may give erroneous values.

In comparing the concentrating ability of the kidneys as measured by the Addis test and that of the use of posterior pituitary extract in tests of urinary concentration, Taylor, Peirce, and Page<sup>7</sup> conclude that substitutes for the Addis test which do not approximate the ceiling of specific gravity are not entirely acceptable in clinical practice.

During the past few years, considerable attention has been given to the relationship of the hormones to renal function, but as yet there is no unanimity of opinion concerning the effect of hormones upon the kidney. Hans Selye (1939), in his experiments on the mouse, found that testosterone caused a marked enlargement of the kidney. Histologically, such kidneys were characterized by pronounced hypertrophy of the epithelium of the proximal and distal convoluted tubules and of the epithelium lining the parietal lamina of Bowman's capsules. While it is too early to draw final conclusions, it is possible that the male hormone causes certain metabolic changes that result in increased kidney function. Then again, this hormone may exert a specific physiological trophic in-

fluence on kidney tissue and in that way it may be possible to improve kidney function by its administration.

In a report on the influence of male sex hormone on the degree of compensatory renal hypertrophy following unilateral nephrectomy, MacKay (1940) found there was a definite increase in degree of compensatory renal hypertrophy. He believes that if testosterone exerts a specific physiological trophic influence on kidney tissue, it may have a favorable influence on the damaged kidney in Bright's disease. Function may be improved by hypertrophy of the renal units which have not been destroyed.

Lattimer (1942) studied the action of testosterone propionate on the kidney and confirmed the renotrophic effect of this hormone. He found the hypertrophy induced was a true increase in tissue solids. Its increase throughout the tubular structure was due to an increase in cytoplasm rather than to an increase in nuclear elements. Renal function in dogs, measured by inulin clearance and diodrast Tm, was increased by testosterone propionate in proportion to the increase in renal tissue. In humans, the largest safe dose of testosterone improved renal function only when combined with the simultaneous compensatory hypertrophy following nephrectomy. No alteration of blood pressure was noted in rats, dogs, or humans while under treatment.

A rapid rise in maximal capacity of the kidney to excrete diodrast occurred in dogs following administration of testosterone propionate (1942). This increase in diodrast Tm may amount to 100 per cent. The change in diodrast Tm is reversible, but the time required for the return to original values varies greatly. The increase in diodrast Tm is accompanied by a reduction in urinary excretion of sodium and potassium,

but the rate of creatinine clearance and diodrast clearance is unaffected.

Klopp, Young, and Taylor<sup>8</sup> investigated the renotrophic effects of *testosterone* and of testosterone propionate in man, using the propionate in amounts comparable on a weight basis with those used in animal experiments. They found that administration of testosterone and testosterone propionate, in amounts presumed adequate for renotrophic effects, did not alter significantly the glomerular filtration rate, renal blood flow, the maximum rate of tubular secretion of p-aminohippurate, or the maximum rate of tubular reabsorption of glucose in four normal subjects or in five patients with impaired renal function.

Thus far investigation on human subjects has failed to show an increase in renal functional capacity, and an increase in the size of the kidney has failed to produce an increase in renal function. Dean, Abels, and Taylor<sup>5</sup> thought the lack of response might be due to one of at least two conditions: (1) On a comparative animal weight basis, the patients received an insufficient amount of testosterone propionate; (2) renal functions affected by the hormone in man may not be the same as those in the dog. To test the effects of testosterone or its propionate on human renal function, they treated two groups with comparatively large doses, ranging from 90 to 300 mg. per day for periods of from eight to twenty-three days. No significant effect was noted in glomerular filtration rate, renal blood flow, effective tubular secretory, or resorptive mass. They felt it was possible that the androgen would not increase normal renal function but that the hormone would return impaired function toward normal levels. To test this hypothesis, large amounts of propionate were given to patients with essential hypertension and chronic

pyelonephritis, all of whom had renal damage. Dosage schedule ranged between 100 and 300 mg. daily for periods of thirteen to thirty-three days. No significant or uniform changes were observed, and the high degree of extracellular water retention induced by daily injection of 300 mg. of propionate made the use of larger doses of the hormone inadvisable.

Since administration of amounts of testosterone or its propionate, which on the basis of animal experiments were adequate, did not alter the renal functions measured, the possibility that species differences exist was entertained. Further investigation was done with pregnenolone, but no renal function was altered significantly. In studying the effect of estradiol benzoate, a depression of tubular resorption of ascorbic acid was obtained, but other renal functions were unchanged. These investigators made two fundamental observations: (1) Species differences do exist; (2) administration of hormones does not affect all renal functions simultaneously.

In studying the administration of estrogen on the mechanism of ascorbic acid excretion in the dog, Selkurt and associates (1943) found that estradiol benzoate increases the clearance of ascorbic acid by reducing tubular resorption. As a result, the rate of excretion is increased, while the plasma level tends to be reduced. During estradiol benzoate therapy, load levels considerably higher than those normally needed for tubular saturation produced a maximal rate of reabsorption, equivalent to normal. In the absence of a change in glomerular filtration rate and with no significant histological changes, it was concluded that estradiol affects the kinetics of ascorbic acid reabsorption. Changes in tubular reabsorption are not attributable to changes in urine pH, hematocrit, or

tubular damage. Changes in water balance, with slight increase in glomerular filtration rate were observed in normal dogs after estrogenic treatment, but not in one castrate. However, all showed a comparable alteration of the renal ascorbic acid mechanism.

### Acute Glomerulonephritis

The mechanism of glomerulonephritis is still an unsolved problem. Nettleship,<sup>9</sup> who studied the etiology of glomerulonephritis, believes: (1) An acute inflammatory disease is the trigger which sets off the series of events resulting in glomerulonephritis; (2) experimental production of true glomerulonephritis in animals, similar in all respects to that seen in man, seems to contradict the above theory. However, the most recent work, connecting the streptococcic etiology with sensitivity phenomena, ties more closely with the human disease than does the antikidney substance work. Glomerulonephritis is intimately connected with streptococcic growth in the body. Some investigators have concluded that both general allergic hypersusceptibility and kidney predisposition are necessary to produce glomerulonephritis. The only experimental nephritis which can be produced consistently and which closely resembles human glomerulonephritis in all morphological and dysfunctional respects is that caused by injection of heterologous antikidney antibodies. However, its usefulness is marred by our inability to produce the disease with homologous or autogenous kidney extracts, a necessary condition to make the work strictly applicable to man.

Cavelti and Cavelti,<sup>10</sup> in their study on the pathogenesis of glomerulonephritis, proposed: (1) To investigate the possibility of a production of autoantibodies to kidney incited by homologous kidney rendered antigenic by combina-

tion with foreign antigens, particularly streptococci and their products; and (2) to ascertain whether any antibodies to kidney formed have the ability to react with the kidney *in vivo* to precipitate nephritis. The studies were carried out simultaneously in rabbits and rats, by means of essentially analogous procedures. Results provide evidence that streptococci are able to confer antigenicity on renal material which is not antigenic in the same species. The underlying mechanism might be explained by the concept of haptens (represented in the kidney) being attached to a "carrier" of protein nature (streptococcus or its substances). Injection of such combinations leads to the formation of antibodies, not only to the streptococcus, but also, and independently, to the kidney of the same species. Such antibodies to normal kidney of the same species were demonstrated by several serological methods: Agglutination of collodion sensitized with kidney extract; agglutination suspensions of renal cells and cell fragments, and precipitation of kidney extract by the serum. Antibodies determined by the collodion method also reacted serologically with kidney from the same animal which furnished the serum.

The hapten mechanism concept is supported by the fact that other antigens, such as staphylococcus toxin, can act as a carrier for the kidney material, rendering it antigenic. It is likely that haptens of nonprotein character were involved in these experiments. Some results indicate that with the immunizing procedures employed, two and possibly more different antibodies reacting with kidney *in vitro* are formed. With respect to the genesis of glomerulonephritis in man, streptococci or their substances might cause a slight toxic damage to the kidney during the height of a streptococcal infection, perhaps dem-

onstrated clinically by albuminuria and other urinary symptoms noted in cases of streptococcal infection. "Undoubtedly, material from such damaged renal tissue could enter the blood stream during the process of reparation, perhaps still attached to the toxin which had acted on it. On reaching the sites of the formation of antibodies, this complex would act as an antigen. Antibodies to kidney would be formed, which, if they reach a sufficiently high level, would precipitate glomerulonephritis by their specific reaction with the hapten represented in the kidney."<sup>10</sup>

A form of focal glomerulonephritis was produced in animals by intravenous injection of a strain of nonhemolytic streptococcus isolated from the stools of a patient with cholecystitis and colitis. The lesions encountered were largely confined to joints, gallbladder, heart, and kidney. All animals received a series of intravenous injections, averaging twenty-four, over a fixed period. Control cases were included. Rehfuess and Nelson<sup>11</sup> believe their findings are significant because nonhemolytic streptococcus of intestinal origin hitherto has not been suspected of playing a part, under appropriate conditions, in the evolution of glomerulonephritis. Apparently, only the viable organism is capable, experimentally, of inducing the effect, since neither the killed organism (vaccine) nor any soluble toxin (filtrate) produced a definite increase in the incidence of lesions.

Binger<sup>12</sup> believes glomerulonephritis is due to an inflammation or toxic reaction of the capillary loops of the glomeruli, which is really an endocapillaritis and an involvement of a part of the vascular system. In the acute form, it may be associated with infections of the upper respiratory tract, tonsillitis, scarlet fever, and other infectious processes. Toxins from the primary infection are



probably the causative factor. In making a diagnosis of glomerulonephritis, Binger believes to rely solely on the presence of albumin, blood, and casts in the urine is not only a hazardous procedure but it may result in the wrong diagnosis. Such diseases as polycystic kidney and chronic pyelonephritis also may cause these urinary symptoms.

*Polycystic kidney* will produce a picture not unlike that of chronic glomerulonephritis. Usually, the course is more benign, and a high concentration of blood urea is better tolerated. Blood pressure is elevated, retinitis develops as the disease progresses, and cardiac degeneration and decompensation are common. *Chronic pyelonephritis* may be mistaken for chronic glomerulonephritis. A history of recurrent infection in the urinary tract, with fever, chills, pyuria, hematuria, and bacteria, usually establishes the diagnosis. As the disease progresses, there is gradual renal impairment with the characteristics of chronic glomerulonephritis: Hypertension, uremia, vascular and cardiac changes, and anemia. *Tuberculosis* of the kidney also may be confused with chronic glomerulonephritis, especially when pus, blood and albumin constantly occur in the urine. A centrifuged specimen of urine should be stained for mycobacterium tuberculosis. Excretory urography and cystoscopy are of invaluable help in diagnosis. A *hypernephroma* may produce albumin and blood in the urine, and usually there are recurrences of gross blood. The malignant lesion may be far advanced before clinical evidence of its presence is uncovered. Early surgical intervention, followed by roentgen therapy offers a favorable prognosis.<sup>12</sup>

In advanced stages, it may be difficult or impossible to differentiate *essential hypertension* from chronic glomerulonephritis. Albumin and urinary sedi-

ment, impairment in renal function, anemia, and degree of hypertension are confusing in their similarity, and end results, such as uremia, cardiac failure, or cerebral vascular accident, occur with equal frequency. However, several points in history and physical examination differ. Often, in chronic glomerulonephritis there is a history of acute nephritis which followed an infection of the upper respiratory tract or other infection. Early in the disease, urinary abnormalities are the dominant features. In essential hypertension, onset, course, and symptoms may vary in intensity and character, and the disease may produce no symptoms or may remain undetected until it is well advanced. However, in many cases of chronic glomerulonephritis, onset may be insidious and the disease may be far advanced before the patient is aware of it. In these cases, with an indefinite history and an insidious onset, differential diagnosis is difficult.<sup>12</sup>

Success in the treatment of kidney diseases depends, not only on the correct diagnosis, but also on the detailed evaluation of the amount of damage suffered by the kidney and on the accurate estimation of the amount of intact kidney substance left, according to Ginsburg.<sup>13</sup> In the diagnosis of acute glomerulonephritis, other types of nephritis must be ruled out, and Ginsburg differentiates the following:

*Acute interstitial nephritis* often occurs with acute infections. The toxin producing the inflammatory infection in the kidney is mild, and only small portions of the interstitial tissue are involved. The disorder is manifested clinically by the symptoms of the acute infection and laboratory findings of albumin, lymphocytes, and red blood cells in the urine. Urine and blood show no evidence of nitrogen retention or other

signs of kidney hypofunction. *Acute focal nephritis* may complicate more severe infections. Pathology consists of inflammatory lesions involving isolated groups of glomeruli. Clinical findings are those of the primary disease, but at the height of infection the patient may pass bloody urine. Urinalysis shows evidences of kidney damage, such as albumin, blood, and casts, and, at times, micro-organisms, but no evidence of kidney hypofunction. Blood shows no nitrogen retention; urea clearance test is normal.<sup>13</sup>

*Embolic nephritis* complicates subacute bacterial endocarditis, and the lesions consist of microscopic emboli lodged in the minute capillary loops, producing small infarcts. The only clinical findings may be pain in the back and the symptoms of subacute bacterial endocarditis. Laboratory findings show no evidence of kidney hypofunction, although the urine reveals albumin, cells, and casts.<sup>13</sup> Blood cultures are made in suspected cases, and if streptococcus viridans is found, together with cardiac findings, fever, petechia, and general debility, it is assumed that renal findings are secondary to infection in the blood stream.<sup>12</sup>

*Nephritis of pregnancy* presents a nephrotic rather than a nephritic picture; however, it must be considered in the differential diagnosis. Pathological lesions are degenerative and affect the entire nephron, that is, both the glomeruli and the tubules. Laboratory examination reveals massive albuminuria and casts.<sup>13</sup>

Clinical findings are absent and laboratory examination reveals nothing in *senile nephrosclerosis*, because kidney damage is negligible and the metabolic activities of patients past fifty years of age are small. Pathology consists in atherosclerosis of the larger renal arteries. As this process advances, the

lumen of the branches of the renal arteries becomes narrowed; nourishment to the wedge-shaped areas of kidney substance is diminished and finally cut off. Such areas become fibrosed; their glomeruli become hyalinized and functionless. The efferent arterioles, which no longer carry blood to the tubules, degenerate and are replaced by connective tissue.<sup>13</sup>

Ginsburg<sup>13</sup> considers *acute glomerulonephritis* the first of three stages in the development of progressive renal disease. This stage, which affects the glomeruli, is one of congestion, exudation, and proliferation. Clinical manifestations are: (1) Lower back pain; (2) edema; (3) slight rise in blood pressure; (4) anemia. Laboratory findings are due to the damaged filter of the glomeruli and to the completely occluded glomeruli and their degenerated tubules: (1) Oliguria; (2) albuminuria; (3) high specific gravity; (4) red blood cells; (5) casts of many varieties.

Degeneration and proliferation characterize the second stage, *chronic parenchymatous nephritis*. Clinical findings are: (1) Edema, mild or severe; (2) progressive anemia; (3) hypertension. Laboratory examination reveals the amount of damage and remaining function: (1) Massive albuminuria; (2) high specific gravity; (3) reduced sodium chloride in the urine; (4) casts of all varieties; (5) evidence of anemia; (6) high cholesteremia; (7) lowered plasma proteins; (8) nitrogen retention may be normal; urea clearance abnormal; (9) low basal metabolic rate.

The third stage, *chronic interstitial nephritis*, is one of atrophy and scarring. In the transition from stage two to three, which may take some time, these changes occur: (1) The walls of the glomerular arterioles thicken; (2) glomeruli shrink and become hyalinized;

(3) tubules atrophy, degenerate and are replaced by connective tissue; (4) other tubules dilate, reach out above the surface of the kidney and give it a granular appearance; (5) the cortex narrows; the kidney shrinks, whitens, contracts; (6) ischemia of the kidneys becomes more marked; more renin is produced to cause an increase in blood pressure; (7) hypertension in turn causes a widespread arteriosclerosis, affecting many vital organs.

The most important clinical finding is hypertension, which serves a compensatory purpose as it forces through the remaining intact and hypertrophied glomeruli large quantities of urine, carrying off enough nitrogen waste products to maintain a normal blood urea. Other clinical findings are polyuria, edema, and the complications of hypertension. Laboratory findings show: (1) Albumin is reduced to a trace with the obliteration of so many damaged nephrons; (2) specific gravity falls due to diminished albuminuria and polyuria; (3) casts decrease or disappear; (4) cholesterol returns to normal levels; (5) renal insufficiency is manifested by low urea clearance and high urea nitrogen retention, which antecede the terminal stage, uremia.

Kempner<sup>12</sup> reports the use of a *rice diet* in the treatment of 213 patients with acute or chronic primary kidney disease or with hypertensive vascular disease, with or without cardiac involvement, retinopathy, or uremia. In addition to rice, *sugar, fruit and fruit juices, vitamins, and iron* were given. Later, the diet was supplemented with *vegetables*, small amounts of *meat*, and *eggs*. He found subjective improvement, decrease in nonprotein nitrogen retention, diminished heart size, improvement in vascular retinopathy, disappearance of edema, and decrease in abnormalities of the electrocardiogram. The blood

pressure of 107 hypertensive patients decreased, on an average, from a level of 200/122 to 149/96, after an average of 62 days on the diet. In sixty other hypertensive patients, there was no significant decrease in blood pressure.

The management of the various stages of nephritis is discussed by Bradley.<sup>15</sup> To establish a basis of security, he states it is necessary to outline for the patient an intelligible account of his disease, the necessity of the diagnostic procedures he must undergo, and the objectives of therapy. During the *latent stage* of nephritis, the patient should live a normally quiet life. Dietary restrictions are unnecessary except where slight edema persists, in which case salt and water are restricted.

During the *nephrotic stage*, the chief problem is removal of excess body fluids and replacement of plasma protein. Administration of *albumin concentrates* in sufficient quantity to replace losses in the urine seems to be the logical procedure. However, albumin concentrates are not generally available, but one can use whole blood and plasma. Although immediate reversal of hypoproteinemia is impossible with the means at hand, this does not mean such measures are valueless. Protein intake must be increased to the point where the urine loss is exceeded. Salt and water restriction fight edema formation. Since anorexia may be a problem, appetizing preparations are of definite value, and adequate vitamin intake is of great importance. Diuretic agents are of value, and whole blood or plasma may be used. Other diuretics, such as *urea*, 60 gm. a day in divided doses; *mannitol*, 25 to 50 gm. a day intravenously in divided doses; *potassium chloride*, 5 to 10 gm. per day in divided doses; *mercurpurin*, 1 to 2 cc. per day intravenously or intramuscularly; *ammonium chloride*,

8 to 12 gm. per day in divided doses, may be used effectively. Never use the latter three diuretics in the presence of renal insufficiency.

In the *terminal stage*, when dehydration becomes a factor, there is failure of water reabsorption with marked water and electrolyte loss. If the thirst mechanism is impaired, increased water intake is prescribed. Where diarrhea and vomiting are present, dehydration may be profound, oral replacement may be impossible or inadequate, and fluid must be given by vein. Combating the resulting acidosis with alkalinizing agents may be effective, but treatment must be conducted carefully. Overtreatment may be as damaging as none. Therefore, doses of *sodium lactate-Ringer's solution* and *sodium bicarbonate* are smaller than those usually given. Proper hydration and correction of chemical imbalances are guided by close observation of the effects, and therapy is directed at achieving an optimal clinical response.

Although acute glomerulonephritis is ordinarily amenable to medical treatment, occasionally surgical treatment is indicated, especially when cases fail to respond to a medical regime.<sup>16</sup> In these cases, destined to a fatal outcome, decapsulation should be performed within twenty-four hours after onset of anuria. Early operation is also indicated in cases with progressive oliguria, increasing edema, and rising blood pressure. Pain and hematuria, uninfluenced by medical treatment, may require decapsulation for relief. Decapsulation is contraindicated in chronic nephritis except in cases of progressive oliguria or anuria or in cases of superimposed nephritis in crises which do not respond to treatment. In genuine lipoid nephrosis, surgery is rarely indicated. Operation is restricted to cases with persistent edema and increasing albuminuria or to recurrent cases which

do not respond to a high protein-thyroid extract therapy. Abeshouse also recommends decapsulation if persistent oliguria or anuria follows sulfonamide therapy, after ruling out the presence of calculi or concretions in the pelvis or ureter by cystoscopy and ureteral dilatation. Early decapsulation is also recommended as an effective method of combating the anuria associated with a posttransfusion type of nephrosis.

### Edema

Edema is an excessive accumulation of interstitial fluid. Its cause lies either in failure of the normal mechanisms of movement of this fluid or in the operation of controls which protect the body from changes in concentration of electrolytes in interstitial fluid by permitting changes in volume, according to Corcoran.<sup>17</sup> Sodium retention is the stimulus which usually provokes fluid controls to permit edema formation. Therefore, *sodium retention* is often the key to the formation of edema. Since the principal site of sodium excretion is the kidney, retention of sodium may be associated with structural or functional disturbances of renal function. In either case, restriction of dietary sodium below the level of sodium excretion eventually results in loss of water and salt and in correction of edema.

### The Sulfonamide Kidney

The danger of sulfonamide therapy lies not only in the immediate toxic manifestations but also in the production of remote effects which may be more serious. Toxic reactions upon the kidney may be the result of the precipitation of the drug or of its acetylated form with formation of renal calculi. Another effect upon the kidney may be a direct nephrotoxic effect. In the nephrotoxic kidney, evidence of renal

involvement may occur in the course of therapy and consist of heavy albuminuria, oliguria, anuria, and nitrogen retention. Fever, dermatitis, or conjunctivitis may be other manifestations of toxicity to the drug. When crystals are absent in the urine, even after catheterization of the ureters, or where an oliguria or anuria develops during therapy, suppression of urine most likely is due to involvement of the kidney itself. The maintenance of a high urine output and an alkaline urine is of great importance in the prevention of urinary calculi. However, it is not an assurance that the nephrotoxic kidney will not result from a course of sulfonamide therapy.<sup>18</sup>

Lehr<sup>19</sup> investigated the possibility of lessening renal damage by employment of sulfadiazine and sulfathiazole mixtures. He found the acute and chronic toxicity of this drug combination for albino rats is strikingly low if compared with the effect of similar or identical total concentrations of either sulfathiazole or sulfadiazine alone. Chemical analyses and postmortem examinations demonstrated a diminution of intrarenal obstruction from the drug precipitate as the chief reason for the low toxicity of the mixture. Lehr suggests the combination of these two compounds, since their application may decrease the danger of renal complications without interfering with the antibacterial efficiency.

Studying the influence of various agents on the production of renal lesions in rats by sulfadiazine, Kornberg *et al.*<sup>20</sup> found that casein, urea, sodium bicarbonate, and sodium chloride exert preventive actions on the development of renal lesions, despite restriction of water intake. Sodium bicarbonate was found to be the most effective agent under the conditions of the study.

The most important factor in causing renal complications is a low urinary out-

put, according to Prien.<sup>21</sup> Development of obstructive concretions depends on two conditions: Hydrodynamics of the urinary tract and affinity of crystals for each other. Sulfonamide crystals form in the convoluted tubules where reabsorption of water occurs. Sedimentation of these crystals occurs in the terminal portions of the collecting tubules and in the renal calyx. Obstruction of the terminal portions of the collecting tubules is caused by aggregation of crystals and formation of concretions. A second type of renal lesion may occur, with a widely disseminated focal necrosis of the kidney tubules, the etiology of which is not an obstructing concretion but a toxic injury to the tubules.

In a study of the incidence of sulfadiazine dysuria, Jepson<sup>22</sup> confirmed its relationship to urinary pH. He found no cases with a pH of over 6.5, and no deposits of sulfadiazine in any urine with a pH of over 7.5. Prophylaxis depends on the control of urinary pH and output, and treatment consists of intensive intravenous fluids with alkalis. This confirms a report by Murphy and Woods (1943) on the relationship of the pH of the urine to the number of crystals present.

### Crush Syndrome

Crush syndrome or ischemic muscle necrosis is to be suspected in cases with a history of burial beneath débris; in those with a large amount of muscle damage; those with severe contusion to large muscle groups or extensive fractures of the spine, pelvis, and long bones accompanied by contused or lacerated muscle; those with obstruction of blood supply caused by pressure from surrounding edematous tissue or direct pressure on main arteries by bone fragments or foreign bodies.

Homan and Brown,<sup>23</sup> in the United States Naval Medical Bulletin, report a case of uremia from toxic pigment nephrosis, secondary to compression of voluntary muscle, possibly resulting from the application of a restraint pack.

Patients with a large amount of muscle damage may appear quite well at first, but within a few hours their condition deteriorates.<sup>1</sup> Plasma leaks out through the damaged capillaries into the necrotic muscle, the limb swells, hemoconcentration develops. While blood pressure may be maintained for a time, perhaps due to the increased viscosity associated with hemoconcentration, eventually vasoconstriction no longer compensates for plasma loss, and there is a sudden fall of blood pressure. With adequate transfusion, the majority of patients recover from this shock phase within eighteen hours. The fall in blood pressure may be forestalled by administration of *saline* and *lactate* solution by mouth or parenterally, reinforced with *plasma*. Plasma is used when blood pressure has already fallen. Shock can usually be accounted for by local fluid loss. It is of the same clinical severity as that due to loss of equivalent amounts of blood, but unlike hemorrhage, plasma leakage begins and ceases gradually. The affected limb becomes swollen and brown; peripheral arterial pulsation may disappear, perhaps due to increase of pressure in the deep compartments. Circulation may return spontaneously or after incision of the deep fascia with release of tension.

Bywaters<sup>1</sup> states that the initial urine examination may reveal very little. Later, the urines are highly acid and contain albumin, creatine, and muscle pigment. If renal failure has set in, urine is scanty, of low specific gravity and contains little pigment. The urine composition tends toward that of glomerular filtrate; urea

concentration decreases; chloride concentration may rise, even with low plasma levels. Toward the end of the first week, daily output and urea concentration may increase. But, unless a large diuresis sets in, the patient will die about the sixth or seventh day with nitrogen and potassium retention. In patients who develop renal failure and recover, albuminuria lasts longer than pigment excretion. Function returns to normal within six months. If renal damage is prevented, the urine is less acid, without deposit, and of a bright red color due to the presence of oxymyohemoglobin in solution. Very mild cases show only a trace of pigment, albumin, and creatine, with no depression of renal function.

The treatment advocated by Bywaters<sup>1</sup> is as follows:

As renal failure, once developed, is very resistant to treatment, the first aim is to prevent its development. This is attempted: (1) By preventing a fall in renal blood flow. Transfusion of plasma and crystalloid solutions, such as saline or lactate, is indicated to restore lost plasma and extracellular fluid; (2) by maintaining a high rate of flow of dilute alkaline urine, by forcing fluid by mouth from the earliest possible moment. Sodium bicarbonate, 1 teaspoonful to the pint, is repeated hourly. Hydration and alkalization can be most rapidly achieved by the use of isotonic sodium lactate with glucose-saline, intravenously. If a diuresis is not soon obtained, renal damage is probably already present, and further forcing of alkali and fluid is dangerous, since alkalosis develops readily in patients with renal failure. Urine reaction changes from acid to neutral only slowly when renal function is impaired; if, therefore, an alkaline diuresis is not obtained in the first twelve hours despite alkali therapy, it is stopped. In success-

ful cases, alkali is given at a rate sufficient to keep the urine alkaline for as long as pigment is being excreted (24 to 48 hours). Such treated cases, severe enough to produce high grade renal failure if untreated, put out large quantities of muscle pigment and so forth without developing nitrogen retention.

The use of citrate to produce alkalization is not without danger because of its calcium-binding property. Whether given by mouth or by other routes, the salt must be that of sodium, not of potassium, since potassium poisoning is easily produced in the uremic state.

While most deaths before the sixth day are due to failure to transfuse plasma or to associated injuries, Bywaters continues, some have been due to overloading the circulation. Watch must be kept on neck veins and lung bases.

Use of pressure bandages to limit plasma loss has been advocated, but this is potentially dangerous, since the increase in intramuscular pressure, probably osmotic, due to autolysis, may be adequate to obliterate traversing blood vessels against the encircling fascial sheaths. Tight binding would only increase this tendency. The injured limb, if ischemic, is kept cool. This will decrease the rate of autolysis and allow living tissue to survive on a smaller margin of blood supply. Immobilization is also needed. Theoretically, decapsulation should be successful in established renal failure, but in practice it has not been found so.

Parsons<sup>24</sup> reports two cases of traumatic uremia. Both patients were healthy young soldiers whose wounds caused such extensive muscle and vascular damage as to require amputation. The severe shock was treated by transfusion of blood and plasma. Uremia developed rapidly and was responsible for the death of one patient, since his wounds were

not serious enough to cause a fatal outcome.

Discussing the changes which may occur in compressed areas, Magnier<sup>25</sup> summarizes them as: Compression, ischemia, muscle necrosis and autolysis, decompression, loss of fluid from the circulation into the tissues (with secondary hemoconcentration), liberation of powerful toxins into the local tissues and into the general circulation, development of bruising, erythema, edema, and vesiculation in crush cases.

Another clinical syndrome, not unlike the above, is that commonly seen in the patient in shock. Van Slyke *et al.*<sup>26</sup> state that the most frequent cause of clinical shock is a deficit in the volume of circulating blood, which deficit may result from hemorrhage, external or internal; from seepage of plasma from burned surface areas or injured intestines; from the dehydration of vomiting, dysentery; or from other dehydrating conditions. If loss of circulating fluid or the accompanying trauma is not severe enough to cause death at once, a constriction of the peripheral circulation occurs, which is the most striking visible sign of the condition called shock. There is a constriction of both the main arteries and the smaller vessels in the skin and extremities.

In dog experiments, they found that when trauma was severe, renal blood flow was reduced greatly and excretion of urine practically ceased. The progressive effect of ischemia on the kidney is divided into three stages: (1) Reduced renal function without damage to nephrons; (2) reversible damage to the nephrons; (3) irreversible damage to nephrons. All stages appear to occur in man as a result of a decrease of blood volume.

The shock kidney may develop in nontraumatic clinical conditions, such

as severe dehydration, if they produce prolonged constriction of the renal circulation. The practical conclusion is that, in shock from deficient blood volume, the factor of time in restoring the volume of circulating blood and in overcoming the vascular constriction is all important. Every minute constriction is continued beyond a certain duration adds to the injury to the kidney and other organs and increases the probability of a fatal outcome.

Maegraith *et al.*,<sup>27</sup> in an article on a renal syndrome, possibly induced by renal anoxia, state that it is a condition of impaired renal function with or without anuria or oliguria, developing usually in an acute illness and often associated with transient peripheral circulatory failure. Three causes of this syndrome have been suggested: (1) Mechanical blockage, which does not account for similar cases of anuria in which pigment is absent. It has been generally abandoned; (2) a "nephrotoxic" effect of some injurious substance carried to the kidney by the blood stream; (3) renal anoxia, the main cause of renal damage being temporary deprivation of oxygen.

### Hepatorenal Syndrome

More and more attention is being given to the so-called hepatorenal syndrome. As pointed out by Bradley,<sup>2</sup> there are two viewpoints concerning the syndrome: (1) Following biliary or hepatic surgery, or any extensive gastrointestinal operation, a profound derangement of liver function may result in liver death, characterized by fever, coma, and shock and rapidly fatal. If the course is slower, renal damage occurs and death results from uremia associated with jaundice and hepatic failure. This is the hepatorenal syndrome. (2) Liver death is a disorder resulting from over-

whelming sepsis or from obscure infection rather than from liver dysfunction. However, in either case, the kidneys are damaged by toxins which may be released from damaged liver or which may accumulate as the result of lack of hepatic action.

Barclay and Cooke<sup>28</sup> report a characteristic case of the hepatorenal syndrome and emphasize some important points in therapy. The cause of the failure of liver and kidney function in their patient is obscure, but it is concluded that choline was the causal factor in the restoration of kidney and liver function. Intravenous choline therapy causes severe sweating, bronchial secretion, and painful abdominal cramps. For this reason, it is dangerous to give to severely ill patients unless bronchial secretions can be prevented.

### Hypertension

Many classifications of hypertension exist, and recently Sloan,<sup>29</sup> in "The Pathogenesis of Hypertension," suggested a classification on five physiological factors which, he states, operate in the human body as blood pressure determinants: (1) Pumping action of the heart; (2) viscosity of the blood; (3) elasticity of the arterial walls; (4) quantity of blood in the vascular tree, and (5) peripheral resistance.

(1) In hypertension due to alteration in the pumping action of the heart, Sloan says three clinical findings are evident: (a) Increase in systolic pressure; (b) low or normal diastolic pressure; (c) an obvious increase in pulse pressure. The principal cause of increased blood pressure is increased cardiac output, which in turn is due to an increased minute volume of the heart. The minute volume is determined by two variable factors: Cardiac rate and the amount of venous return to the heart. Examples of type



one are thyrotoxicosis, arteriovenous aneurysm, aortic insufficiency, heart block.

(2) In hypertension due to increased viscosity of the blood, Sloan mentions polycythemia vera, which, although a rare factor in the production of hypertension, still may increase blood pressure. (3) Hypertension due to a decrease in elasticity of arterial walls is a condition in which the arteries undergo atheromatous and calciferous changes with a loss of elasticity. Because of this, they become less able to "give" with each systolic ejection of blood, and systolic pressure rises. Likewise, these inelastic vessels lose the power of "clamping down" on the smaller diastolic volume of blood, and diastolic pressure falls, remains constant, or rises only slightly. Patients with pressures of 200/90 and with little evidence of renal damage or cardiac enlargement, but with evidence of arteriosclerosis are examples.

(4) Hypertension due to increase in blood volume is exemplified in coarctation of the aorta, which is a local increase in blood volume. A generalized increase in circulatory volume is seen in conjunction with infusions of hypertonic or protein-containing solutions and in pituitary and adrenal disorders. (5) In hypertension due to an increase in peripheral resistance there is an arteriolar constriction which may be nervous or humoral in origin. In the presence of a constant driving force and an increased peripheral resistance, the pressure in the arterial system must rise to maintain the relationship between arterial inflow and outflow. This type of hypertension is characterized clinically by an increased systolic and diastolic pressure with a variable pulse pressure, depending upon the relative degree of change of the two preceding factors.

Rytand<sup>30</sup> discusses the clinical relationship between arterial hypertension and the kidneys and states there are three ways by which hypertension and the kidney may be related: (1) Renal lesions might cause arterial hypertension; (2) hypertension might result in renal disease; (3) still other disorders might simultaneously damage the kidneys and elevate the blood pressure. In the first group, renal diseases causing hypertension, he includes glomerulonephritis, polycystic kidney, pyelonephritis, and urinary tract obstruction. He does not believe renal ischemia is responsible for hypertension since, in patients with glomerulonephritis, indirect estimations of renal blood flow seem to indicate hyperemia; there is no satisfactory explanation for the usual failure of amilydosis, the lesions of multiple myeloma and subacute bacterial endocarditis and some varieties of chronic renal disease, such as the nephrotic stage of glomerulonephritis, to elevate arterial pressure.

Essential hypertension follows gross renal disease in only a small proportion of hypertensive patients and is even more rarely associated with other etiological factors. If a careful examination reveals no cause for elevated diastolic pressure, the patient may be said to have essential hypertension. Recent studies emphasize the fact that organic disease of the central nervous system in man and in experimental animals may be followed by an elevation of arterial blood pressure.

Under the heading of hypertension causing renal disease, Rytand says that vascular changes are associated with hypertension of any cause and are often prominent in the renal vessels. The renal arterioles presumably participate in the generalized systemic arteriolar constriction which causes hypertension, and increased arterial pressure initiates or accelerates atherosclerosis. In essential

hypertension, renal arteriosclerosis accompanies sclerosis of cerebral, retinal and cardiac vessels, although the hypertension arose elsewhere. This produces abnormal results when renal blood flow and other functions are measured by modern methods. Although renal arteriosclerosis is not often the factor causing death in uremia, it is the lesion responsible for the abnormal urine of most hypertensive patients.

Hypertension in renal disease may be associated with a third factor, such as is found in cases of periarteritis nodosa, acute glomerulonephritis, intercapillary glomerulosclerosis, or the patient in pre-eclampsia. Very little is known about this state, in which the blood pressure and the kidney are involved with a third process.

In the differential diagnosis of a patient with hypertension, a family history of hypertensive disease or kidney disease is often significant. The personal history of the patient is carefully heard for its clues to proper management.<sup>30</sup> The early life history of the patient who develops increased arterial tension often reveals phenomena which may be caused by vasomotor instability — such conditions as blushing, flushing, cold, sweaty cyanotic hands, fainting and dizzy spells. The patient is high-strung, sensitive, and reacts markedly to insignificant stimulus. Later, he matures into an ambitious, meticulous, exacting person with the ability to accomplish much in a short time. These early symptoms closely resemble the symptoms of psychoneuroses, a disease of psychogenic origin. In both, great emotional conflicts arise from the ordinary incidents of life; trivial incidents provoke marked reaction. The early life of the patient and his present status are studied, for a readjustment of maladjustments and

environmental difficulties is sought to help the patient.<sup>31</sup>

The subject of differential diagnosis between glomerulonephritis and malignant hypertension was taken up by Murphy.<sup>32</sup> In addition to some of the more common differential points enumerated, he emphasized the fact that anemia is more apt to occur early in glomerulonephritis, whereas, in malignant hypertension, it may occur late in the disease or not at all.

Physical examination serves two purposes.<sup>30</sup> It enables one to find the cause of the hypertension and to evaluate the damage done by hypertensive disease. Laboratory aids which help in establishing a diagnosis in patients with renal disease and hypertension are: Examination of the urine; a simple test of renal function; and pyelograms by intravenous injection of a contrast medium.

Grollman,<sup>33</sup> discussing the experimental basis for the pathogenesis and treatment of renal hypertension, states that many cases of hypertension, particularly of the essential type, are renal in origin and are mediated through a humoral mechanism. He believes the view that chronic hypertension is caused by the circulation of a pressor substance liberated by the diseased or ischemic kidney is contrary to these experimentally demonstrable facts: (1) Pithing a hypertensive rabbit abolishes the hypertension but injection of renin still elicits a rise in blood pressure; (2) unilateral nephrectomy in animals induces the same elevation of blood pressure as does an operation on one kidney; (3) removal of a kidney (experimentally made hypertensive) fails to abolish hypertension; (4) hypertension may exist in the absence of all renal tissue in the parabiotic animal; (5) in chronic hypertension, there is no increase in the amount of pressor substances of the blood, nor

a deficiency of hypertensinase, the enzyme which, *in vitro*, causes destruction of this pressor substance.

In a study of the effect of transitory complete constriction of the human renal artery on blood pressure and on the concentration of renin, hypertensinogen, and hypertensinase of renal arterial and venous blood, Quinby and associates<sup>34</sup> demonstrated that the renal humoral pressor mechanism is stimulated to activity in man as in animals by constriction of the renal artery.

Further studies on normal subjects and on patients with hypertension revealed no justification for considering that the blood pressure is high in human hypertension because of a deficiency of hypertensinase in plasma.<sup>35</sup> The same investigators, Haynes and Dexter,<sup>36</sup> corroborated the evidence that the principal site of formation of hypertensinogen is the liver.

Gregory *et al.*<sup>37</sup> devised a method of bioassay of vasoconstrictor substances. They came to these conclusions: That angiotonin may be demonstrated in the ultrafiltrates of plasma from patients with blood pressures elevated by intravenous injections of angiotonin; that ultrafiltrates of plasma from normal and from hypertensive patients contain a nearly identical amount of vasoconstrictor substance(s); that ultrafiltrates of blood plasma from patients made transiently hypertensive by angiotonin contain a far greater amount of vasoconstrictor substance than ultrafiltrates of plasma from hypertensive patients; that plotted curves of vasoconstrictor effects of ultrafiltrates of plasma from normotensive and from hypertensive persons are identical and differ in character from curves of vasoconstrictor effects of angiotonin in frog Ringer solution or in ultrafiltrates of plasma to which angiotonin has been added; that angiotonin

is not present in increased amounts in the blood of patients with essential hypertension of long duration; that in essential hypertension of long duration, the elevation of blood pressure is not due to increased production of angiotonin.

Hypertension not only produces changes in renal arteries but also in the blood vessels of the heart, and, until there is a clearer understanding of its cause and its exact relationship to arterial sclerosis, it will be impossible to describe the exact changes produced by it alone on the heart.<sup>38</sup> However, in long-standing hypertension, there is usually sclerosis of the coronary arteries as well as of the aorta. In many cases of hypertension with coronary disease, it is impossible to separate the effects of one from the other; but, in cases of sclerosis with associated hypertension and with no other complications, any lesion other than the sclerotic changes may be assumed to result from hypertension. In general, Luten<sup>38</sup> concludes, hypertension tends to produce cardiac enlargement, while coronary disease has no such tendency. Both hypertension and cardiac disease, however, can and do impair ventricular function and thus induce heart failure. Many patients with hypertension of long standing suffer few clinical evidences of cardiac involvement. Others, with greater degrees of coronary disease, or because of other circumstances, exhibit more serious cardiac signs and symptoms at various times. Often, roentgen ray, electrocardiogram, and physical findings remain conspicuously abnormal for years without important symptoms, or with long intermission of serious symptoms.

In a discussion of hydronephrosis and hypertension, Hinman<sup>39</sup> says experiments on the flow of blood and on general hypertension indicate that hy-

pertension does not increase the rate of progress of hydronephrotic atrophy. Hydronephrosis develops in individuals with essential hypertension according to rule and in no way differently from its development in other patients. High blood pressure has no influence on the development of hydronephrosis, and hydronephrosis rarely causes hypertension. However, the later changes in a kidney which has been repaired for hydronephrosis may cause hypertension.

Nephroptosis *per se* is seldom if ever an etiologic factor in causing hypertension, according to Braasch and Goyanna.<sup>40</sup> In a series of 133 cases of nephroptosis, they found 16 cases of hypertension. In none of these cases was nephroptosis regarded as an etiologic factor, and in the majority of cases, the blood pressure was average or less than average.

A criticism of the methods employed by some investigators in the study of the problem of urological diseases as a cause of hypertension is voiced by Rath and Russek.<sup>41</sup> In various studies of the problem, they state investigators failed to include control series, omitted statistical evaluation of results, and used systolic blood pressure alone in defining hypertension. In observations on 357 urologic cases and 654 control subjects, they invalidate the impression that surgical conditions of the urinary tract as a general group are causally related to elevation of blood pressure. Although the causal relationship in individual cases cannot be denied, they were unable to demonstrate an association between urologic disease and hypertension.

Ben-Asher<sup>42</sup> reports a case of renal infarction causing a hypertension which lasted twenty-one days; then disappeared concomitantly with the return of normal renal function. Three more cases of paroxysmal hypertension, caused by

adrenal tumors, are reported by Padis<sup>43</sup> with an excellent discussion of the clinical picture and laboratory findings in this condition.

Treatment of essential hypertension remains one of the unsatisfactory chapters in therapeutics, according to Massie.<sup>44</sup> Fundamental causes are still obscure; one can neither remove nor successfully combat them. In many cases, no methods at the physician's disposal will lower the blood pressure for any significant length of time. In other cases, the blood pressure can be reduced for a long period with beneficial effect. Treatment is symptomatic, rather than ideally etiologic, but in many cases much can be done to influence the course of the disease and to combat its complications.

Lack of understanding of the fundamental nature of hypertension and the difficulty of evaluating the many therapeutic agents used are causes for unsatisfactory treatment of the disorder.<sup>45</sup> The value of therapeutic methods is made difficult by the unpredictability of the natural course the disease will take in a given case and by variations during therapy which are wrongly attributed to the specific effect of treatment. In particular, psychic effects must be recognized, since the condition characteristically responds temporarily to any form of therapy; this universal psychological response has been the source of false hopes built about a multitude of drugs and devices.

The drugs commonly used in the treatment of hypertension today are the sodium and potassium salts of sulfo-cyanic acid, known as *sulfocyanides* or *thiocyanates*. The mechanism of blood pressure reduction has not been established, but vasodilatation through relaxation of smooth muscle and reduction in tissue oxidation appear to be the principal factors.

Toxicology has been summarized by Beamish and Adamson:<sup>45</sup> (1) Reduced blood pressure, which has been held responsible for the production of angina in a few cases, and which may account for part of the weakness and fatigability encountered in early treatment; (2) idiosyncrasy to the drug; (3) direct toxic effects, which may be minor at presumably safe blood levels (8 to 14 mg. per 100 cc.) or major with higher blood concentrations. Minor toxic symptoms include: Weakness and fatigue; aching muscles; irritability, vertigo, drowsiness, lethargy; rhinitis; thyroid enlargement; pyrosis, abdominal discomfort, anorexia, nausea; mild dermatitis; falling hair; decreased libido. Major toxic effects include: Cerebral symptoms (aphasia, slurred speech, unsteady gait, hemiplegia); toxic psychosis; cardiac symptoms (angina pectoris, coronary occlusion, congestive heart failure); severe vomiting and diarrhea; exfoliative dermatitis. Symptoms of fatigue, weakness and lethargy are frequent during the first weeks of treatment. As a rule, they are not contraindications to the drug, although the dose may be moderated.

Beamish and Adamson also treated ten patients with sodium thiocyanate. Optimum blood level was 8 to 12 mgm. per 100 cc. Objective and subjective improvement definitely attributable to the action of thiocyanate was obtained in over half the cases. Blood pressure reductions for all cases averaged 40.5 mm. systolic; 19.8 mm. diastolic. Symptomatic improvement occurred in six cases; mild toxic effects in five. One case developed a transient congestive heart failure. Best results were secured in cases with severe symptoms associated with the least cardiovascular and renal damage. By proper selection of

cases, the authors believe, the number of good results may be increased.

del Solar and associates<sup>46</sup> report another case, the seventh thus far recorded, of death due to the use of potassium thiocyanate in the treatment of hypertension. A distinct fault in dosage on the part of the patient was responsible for the intoxication. They emphasize the danger of prescribing the drug in easily inaccurately measured forms, like the solution for drop administration used in this case.

Using a diet rendered low in sodium content by dialysis, Reichsman<sup>47</sup> found that blood pressure was reduced decidedly in rats with experimental renal hypertension. He proved that prolonged administration of such low sodium diets not only was not deleterious but prolonged the life of the experimental hypertensive animal. In six human hypertensive patients, a drastic reduction in sodium intake, made possible by dialysis of milk included in the diet, resulted in no decline in blood pressure in one subject; a reduction of pressure to essentially normal levels in two; and a moderate reduction in the remaining three, one of whom displayed acute circulatory collapse which responded promptly to sodium chloride therapy. Reichsman suggests such diets be utilized for a brief trial period for patients with hypertension and employed for a longer period in subjects who show a favorable response.

Lazarus<sup>48</sup> believes removal of an involved kidney will result in more or less prolonged reduction in blood pressure in a select group of patients. At present it is virtually impossible, he says, to state with any degree of certainty, prior to treatment, which patients will or will not respond to treatment. A study of the literature indicates that the chance of success is greater in cases of aneurysm of the renal artery, certain types

of renal trauma which lead to impairment of circulation, and in primary unilateral atrophic pyelonephritis. However, in the majority of patients with renal disease associated with hypertension, a mixed group exists where urologic lesions are superimposed upon pre-existing nephritis. In this group, some benefit can be obtained by conservative urologic treatment. The routine consists of periodic *ureteral dilatation* and *pelvic lavage*, and judicious use of *potassium thiocyanate*. The latter, of course, is not employed in patients with impaired renal function.

Continuous caudal anesthesia, produced by a 1.5 per cent solution of metycaine, was used on twenty-five hypertensive patients as a selection test for sympathectomy.<sup>49</sup> The upper level of skin anesthesia was maintained in the region of the fifth or sixth thoracic segments. By this means, transient nerve block was obtained, of strikingly similar distribution to that permanently secured by surgical sympathectomy. Eighteen of the twenty-five patients showed an appreciable fall in blood pressure to normotensive or hypotensive levels. The response suggested a "neurogenic" origin of the hypertension. In seven patients there was little or no alteration in blood pressure, implying a humoral origin of the essential hypertension. Lumbodorsal splanchnicectomy was performed on five of the neurogenic hypertensives and on two of the essential hypertensives. The caudal anesthesia test predicted accurately the outcome in all seven, and the levels of blood pressure obtained under caudal anesthesia showed a striking correlation with the blood pressure readings following surgical sympathectomy.

During the last six years, Smithwick<sup>50</sup> operated on over 600 unselected patients for hypertensive cardiovascular disease. In a series of 179 unselected

patients, observed from one to five years, the majority were improved. Favorable changes in eyegrounds, electrocardiogram, and cardiac and renal function, as well as improvement in general well being were noted. In 42 per cent, the diastolic blood pressure was lowered 30 mm. of mercury or more; in 18 per cent, 20 to 29 mm.; in 20 per cent, 10 to 19 mm.; and in 12 per cent, 0 to 9 mm. Blood pressure was higher in 8 per cent. Smithwick says the characteristic effects of lumbodorsal splanchnicectomy are: (1) Lowering of diastolic levels; (2) narrowing of pulse pressure; (3) reduction in ceiling levels after stimulation; (4) reduction in the magnitude of reflex responses. These changes, in various combinations, were noted in most cases after operation. Certain factors appear to have a bearing upon the outcome. Results indicate women are better subjects than men. From groupings made according to the width of pulse pressure, it is apparent that the wider the pulse pressure, the higher the percentage of poor results. Other factors must be considered in the prognosis for an individual patient: (1) The patient is classified according to preoperative resting diastolic level and according to age; (2) the state of the brain, eyegrounds, heart, kidneys, and response to sedation are determined; (3) the duration of hypertension is important. From these experiences, it is evident that an adequate surgical procedure upon the autonomic nervous system is of real therapeutic value in the management of hypertensive cardiovascular disease.

Ilyman and Leiter<sup>51</sup> report two cases in which blood pressure dropped from 210/130 to 122/86 and from 230/150 to 130/90, following nephrectomy. Both subjective and objective improvement followed operation. It is the authors' belief that all patients with essential

hypertension should have a urological examination with renal function tests where unilateral disease is noted. It is difficult to tell preoperatively which patients with essential hypertension and unilateral kidney disease will show improvement in arterial tension following nephrectomy. Where a nephrectomy is decided upon for the existent nephropathy, a lumbar sympathectomy should be done at the same time on the side of the nephrectomy. If no improvement occurs, a sympathectomy can be considered on the opposite side.

The case of a child who exhibited the features of malignant hypertension which was corrected by nephrectomy was reported by Kennedy *et al.*<sup>52</sup> Since the blood pressure has remained normal for five years, they believe it is reasonable to conclude the cure is permanent. These observations suggest that the prognosis for malignant hypertension in the cases of children who have unilateral atrophic pyelonephritis may be unusually good, because the pathological processes are usually reversible.

Levy, White, Stroud, and Hillman,<sup>53</sup> in an analysis of medical records of 22,741 officers of the United States Army, state that in the group with transient hypertension there was a greater incidence of later sustained hypertension and higher rates for retirement and for death with cardiovascular-renal diseases. The data given, they believe, lend support to the view that transient elevations of blood pressure, above the upper range of normal, often represent an early stage of hypertensive vascular disease.

The same records were used in a statistical analysis to determine the prognostic significance of transient tachycardia.<sup>54</sup> The group with transient tachycardia showed higher rates for later sustained hypertension and for retirement with cardiovascular-renal diseases than did

the control group. The rates were similar to the group with transient hypertension. The death rate with cardiovascular-renal disease was not significantly higher than in the controls. When both transient tachycardia and transient hypertension were present, the incidence of later sustained hypertension was more than twice as great as when either condition was present alone. Transient tachycardia, due to emotional disturbance or some other cause not discernible, like transient hypertension of similar origin, is often a precursor of hypertensive vascular disease. In this respect, the two conditions are of equal importance.

In a sample of 695 men who had experienced at least a year of desert warfare, resting pulse rates, blood pressure, and hemoglobin were recorded. A symptomless hypertension was found in 27 per cent. When 33 of the hypertensives were reexamined after two months of freedom from battle anxieties, 28 showed a normal pressure. Graham<sup>55</sup> suggests the tendency shown by the large proportion of the cases, reexamined after two months, to return toward normal blood pressures, though the environmental conditions were not changed except that personal anxiety had been relieved, favors a neurogenic origin of the hypertension.

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## METABOLISM

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### Insulins and Insulin Mixtures

One of the most investigated aspects in the field of diabetes in the past year has been that in regard to action of the various insulins and more particularly the insulin mixtures used and their respective effectiveness. The object of this work, particularly in regard to insulin

mixtures, has been to devise an insulin combination which will control the severe diabetic by the usual definition of control and at the same time avoid repeated and multiple injections. Unfortunately, as has been pointed out by Adlersberg and Dolger,<sup>1</sup> difficulties have arisen, particularly in the practical use



of *protamine zinc insulin*. One group of clinicians tolerate pronounced glycosuria as long as ketosis, loss of weight, and the usual increased thirst and polyuria were eliminated; whereas, the other group of physicians, and probably the majority, have still made the attempt to keep the blood sugar somewhere within normal limits, adhere to a definite dietary regime, and keep the urine as near sugar-free as is possible. This last matter of keeping the urine sugar-free is probably impossible in the severe diabetic when long-acting insulins are used, as it has been our experience that a small amount of sugar will be spilled in the urine at some time during the day. To keep the diabetic in adequate control and also to avoid multiple injections of insulin have incited the investigative work along the lines of insulin mixtures. Aldersberg and Dolger have summarized the various proposed mixtures of regular and protamine zinc insulin and found the ratio varying between the regular and protamine zinc insulin from three to one to one to three. They have presented a study of 1131 patients, 611 of which were treated with insulin, the others being controlled by diet alone. Of this number, 79 per cent were adequately controlled on protamine zinc insulin, 80 cases or 13 per cent, representing the more severe diabetics, were treated with mixtures of regular and protamine zinc insulin. The diets used in control of these patients were within the usual accepted limits and they found that of the 80 patients using insulin mixtures, 44 per cent were treated with mixtures of regular and protamine zinc mixtures one to one, 35 per cent on surplus protamine mixtures, and 21 per cent on surplus regular mixtures. In all of these cases, only a single daily injection was given and as a result they felt very definitely that insulin mixtures represented a dis-

tinct advance in the treatment of the severe diabetic and that the advantage lay in the flexibility and adaptability to the needs of each patient.

Peck and Schechter<sup>2</sup> have studied very carefully 150 cases and found that such a mixture of regular and protamine insulin controlled 140 out of 150 cases very adequately and that 10 cases were controlled on a modified protamine zinc insulin. They feel that the most frequently used mixture is that of two parts regular insulin, one part protamine, and that the three-to-two mixture of regular to protamine is the next most frequently used. In a few patients, however, mixtures of three-to-one and four-to-one regular insulin to protamine zinc insulin were necessitated to control the extremely severe diabetic. They feel very definitely that the adjustable mixture of regular and protamine zinc insulin is most effective in the control of the severe diabetic and that the mild diabetic is usually very well controlled on protamine zinc insulin alone.

Colwell<sup>3</sup> has likewise studied the varying insulin mixtures and finds that those most effective in the great majority of patients contained at least as much regular as protamine zinc insulin and usually more; sometimes this ratio being five to one of regular and protamine zinc. MacBryde and Reiss<sup>4</sup> have studied the mixture of crystalline and protamine zinc insulin and found that it gave fairly good control in some cases but that, by and large, the results were unpredictable and feel that the modified protamine zinc insulin, which is as yet not available commercially, is much more satisfactory as it usually prevented the after-breakfast rise in the blood sugar and at the same time did not precipitate a hypoglycemic reaction later in the day.

**Modified Protamine Zinc Insulin—**MacBryde and Reiss have reported on

modified protamine zinc insulin and compared it with globin zinc insulin mixtures. They point out a very frequently mentioned disadvantage with globin zinc insulin, that it has a tendency to hypoglycemic reactions in the afternoon when sufficiently large doses are given to control after-breakfast hyperglycemia. In order to obviate this difficulty, they have pointed out that if 20 per cent of the carbohydrate is given at breakfast, 40 per cent at lunch, 10 to 15 per cent at 3:00 P. M., and 40 per cent at supper, the after-breakfast rise will be diminished and the hypoglycemic reactions in the afternoon will be eliminated. They further point out that such a diet does not approximate normal and would be extremely difficult for the average diabetic to follow. It has been their experience as well as that of most other investigators that, in the mild diabetic, globin zinc insulin would appear to be perfectly adequate in maintaining control, but in the moderate or severe diabetic it gave relatively poor regulation. MacBryde<sup>5</sup> feels that two forms of insulin would be sufficient: a modified protamine zinc insulin which would appear to be able to control the great percentage of diabetics, and a regular insulin, the use of which would be limited to diabetic emergencies and whenever a supplemental dose was necessary. He points out that globin zinc insulin has not satisfied the requirements of an insulin of intermediary activity but has only added to the confusion in the field of insulin dosage.

Jordan,<sup>6</sup> studying twenty cases, concludes that globin insulin is not satisfactory and points out a very practical aspect in that the injection of globin insulin produces more pain at the site injected than the other forms of insulin. On the other hand, Jackson and McIntosh,<sup>7</sup> treating six children with diabetes

mellitus, gave during the control period four doses of regular insulin and then continued to give the morning regular and noon regular, combining the two evening doses and giving one dose of globin insulin with zinc, and found that under this regime all the children remained under good control and that comparative diurnal blood sugars were essentially the same. This study, they feel, indicates that globin insulin with zinc has an action of from twelve to fourteen hours' duration.

Although the above types of long-acting insulins and various insulin mixtures are of great help in the control of the severe diabetic, the authors are inclined to agree with Irwig<sup>8</sup> that no one insulin can be considered ideal for all diabetics. The type which controls one patient so often will not appear to control another so that it is our feeling that each patient must be individually studied and the insulin or insulin mixture to be used adjusted to the given case.

### Thiouracil

In last year's article, the experimental, histological, and clinical aspects were summarized and, although a fair amount of clinical work had been reported at that time, there have since been several much larger series reported and observations made which should be of practical assistance in the management of the hyperthyroid patient with this drug. In view of the fact that thiouracil has shown considerable promise in the treatment of hyperthyroidism and is now commercially available, it would seem appropriate to summarize some of the more recent observations gleaned through continued study in the past year. Williams and Clute<sup>9</sup> have reported a series of 152 cases. Another series of 96 cases has been reported by Fishberg and Vorzimer.<sup>10</sup> Gargill and Lesses<sup>11</sup> have fol-

lowed 43 cases, Reveno,<sup>12</sup> 32 cases, and other smaller series have been noted. Something entirely new in the use of thiouracil has been reported by Raab<sup>13</sup> in which he described its use in the treatment of ten cases of angina pectoris. Equally important have been the observations concerning the toxic complications resulting from the use of thiouracil including fatal cases of agranulocytosis reported by Ferrer, Spain, and Cathcart<sup>14</sup> in New York, and Gargill and Lesses in Boston.

**Selection of Cases**—Most of these investigators agree that the best results are obtained in cases of hyperthyroidism of recent origin. Likewise, they agree that the type case which most readily responds is that of the diffuse, hyperplastic gland. It would seem that the drug is equally effective in the various age groups and in the Williams and Clute series the extremes of age were five years to seventy-two years. Patients receiving iodine prior to the use of thiouracil were much slower to respond and it was the feeling that the results obtained were sometimes not as effective. The use of this drug preoperatively was noted and it was thought to be a very effective agent in quieting down the extremely toxic patient, although it was noted that some of the surgeons felt that technically the operation was more difficult following preoperative thiouracil therapy due to increased friability of the gland and difficulty in controlling bleeding. Williams and Clute stressed as usual careful study and evaluation of the case prior to the use of this drug, citing the degrees of toxicity, presence or absence of exophthalmus, anatomical characteristics of the gland, degree of weight loss, cardiovascular status, basal metabolic rate as important factors to be considered prior to any form of treatment.

**Management**—When this drug was first used, it was thought best to hospitalize all patients receiving it as the toxic effects, particularly those leading to agranulocytosis were duly respected and one felt that constant observation was necessary while giving this drug. After another year's observation and experience, most men now treat a large percentage of these patients in an ambulatory way, hospitalizing only those with other serious complications, such as major cardiovascular disorders, diabetes mellitus, and other allied diseases. Whether ambulatory or hospitalized, these patients when receiving thiouracil should have routine blood counts with particular attention being given to the leukocytes. Basal metabolic rates should be done at regular intervals to assist in evaluating results. The authors feel that the blood cholesterol determination is sometimes a valuable index regarding the effectiveness of treatment and it has been their experience that a gradual elevation of the blood cholesterol level usually is concomitant with clinical improvement. In the extremely jittery, nervous, toxic patients, phenobarbital and such sedatives are usually indicated, gradually being decreased in dosage as therapeutic response occurs. Williams and Clute advocate the use of *vitamin B* and *brewer's yeast* tablets as being helpful in the prevention of agranulocytosis. Fishberg and Vorzimer suggest *pyridoxine, vitamin B<sub>6</sub>*, in prophylactic doses of 150 mg. daily by mouth, or 200 mg. intravenously, where there is a significant drop in the leukocyte count. The authors cannot overemphasize the importance of routine blood counts and feel strongly that any significant drop in the leukocyte count must be eyed with alarm.

**Dosage**—Last year, the usual dosage employed was 1 gm. daily in divided

doses with gradual decrease after the first two or three weeks. Most investigators during the past year have discovered that just as effective clinical response is obtained in giving 0.6 gm. daily in three divided doses. Williams and Clute start with this dosage for the first two weeks and then decrease it to 0.3 to 0.4 gm. daily until the basal metabolic rate has approached normal limits. When this stage is reached, 0.1 gm. is given twice daily for the next two or three months, depending on the clinical findings. They often follow this with a maintenance dose of 0.1 gm. daily indefinitely. Gargill and Lesses start with 0.6 gm. to 1 gm. daily again in divided doses and follow in substance pretty much the same schedule as noted above. Fishberg and Vorzimer give 1.0 gm. daily for three days, then 0.6 gm. daily until the basal metabolic rate is normal and then resort to smaller doses much in the same fashion as noted above.

**Results**--The results of therapy are just as promising if not more so than noted in last year's article. As noted before, the diffuse hyperplastic gland which has been diseased for only a short time usually brings forth the most striking results. Results in glands with adenoma in general are not particularly startling, although exceptions do occur. In the cases studied by Williams and Clute, improvement was noted shortly after the treatment was instituted and the usual subjective symptoms had more or less disappeared in from three to seven weeks. Gain in weight came much slower but, after a period of a few weeks picked up rapidly. When used as a pre-operative medication prior to subtotal thyroidectomy, Williams and Clute found that the toxic manifestations during operation were very obviously less severe in cases treated with thiouracil as compared to those treated with iodine, and

in addition the postoperative course was very definitely smoother. Due to technical objections on the part of the surgeons in respect to increased vascularity and friability, Williams and Clute prepared seven patients with thiouracil for five or six weeks, the last two weeks of which *iodine* was likewise given, and it was thought as a result of this therapy less bleeding and friability of the gland were found as the gland treated with iodine and thiouracil tends to be more colloid and less hyperplastic.

**Toxic Reactions** As has been stressed throughout, toxic reactions do occur with the use of thiouracil and when they occur, unless prompt measure are taken, serious difficulty can be encountered. In the 152 cases reported by Williams and Clute, 26 developed reactions to the drug, 2 of these being agranulocytosis, 6 edema of the legs, 5 urticaria, 4 rash of the skin, 2 allergic arthritis, 2 vomiting, 2 drug fever, 1 diarrhea, 1 enlargement of the submaxillary glands, and 1 case developing a leukopenia without agranulocytosis. Gargill and Lesses report similar cases from their series although they encountered one fatal case of agranulocytosis and two cases of jaundice. Reveno reports similar reactions although he had no fatal cases of agranulocytosis. Other fatal cases have been reported in the literature, death being due to agranulocytosis so that certainly one must show a good deal of respect when using this drug. Williams and Clute have noted that there have been only 4 reactions in the last 100 cases treated, which, they feel, resulted from the usage of smaller initial doses.

When such reactions appear, the drug should be stopped immediately. Very often, if it is discontinued for three or four days and then again started with smaller dosage, treatment can be con-

tinued without toxic reactions. However, if there is a marked fall in the total white blood count, the drug must be discontinued indefinitely. Likewise, if there is a drop below 45 per cent of the granulocytes, Fishberg and Vorzimer feel that the drug again must be discontinued. It is extremely important to caution patients when taking this drug, particularly when being treated as ambulatory patients, to report any complication immediately to the physician.

Recently, Rothendler and Vorhaus<sup>15</sup> reported the use of *penicillin* in agranulocytosis resulting from thiouracil. They report a case in which there had been marked clinical improvement as a result of thiouracil, the basal metabolic rate having fallen from plus 85 to plus 18, but during the second week of treatment the differential white count showed only 45 neutrophils and a total white blood count of 4000. Following this, the patient developed the typical findings of agranulocytosis, temperature of 104° and a white blood cell count of 2400 with a marked drop in the neutrophils. *Penicillin* was given in the dose of 20,000 units every three hours, *whole blood* and *liver* injections were likewise given, and thirty-six hours after the beginning of this episode the temperature was normal, the white blood count had risen to 5300 with 52 per cent granulocytes and in seventy-two hours the white blood count was 7300 with 56 per cent granulocytes and the total dosage of 560,000 units of penicillin was used with an apparently excellent recovery. It would appear from this case and other isolated instances that treatment with penicillin is of benefit in the treatment of agranulocytosis resulting from thiouracil therapy.

**In Angina Pectoris**—A very interesting study of ten cases of angina pectoris treated with thiouracil has been reported by Raab. The rationale of this

treatment resulted from an accumulated mass of physiological data which has tended to show that the old and traditional explanation of angina pectoris being due to acute myocardial anoxia is probably not at all true and that neuro-hormonal factors are probably intimately related to the metabolism of the heart muscle and thus to angina pectoris. The present evidence would seem to support the fact that the thyroid hormone sensitizes the heart to the effects of epinephrine. Interestingly enough, also, is the fact that abnormally high concentrations of epinephrine were found in the heart muscle of patients suffering from angina. Early in the physiological studies of thiouracil, Astwood (1943) felt that thiouracil probably selectively suppressed the formation of thyroxin in the thyroid gland and in theory certainly appeared to be a likely substitute for total thyroidectomy. As a result of these findings, in addition to the wealth of accumulated data previously recorded, Raab treated ten patients with the typical angina syndrome with thiouracil. The dose of thiouracil employed was in general similar to that used in the treatment of hyperthyroidism, although at times smaller. It was interesting to note that this treatment proved particularly effective in seven of the ten patients, four of whom became entirely symptom-free during the treatment. Of the three that did not respond, two died subsequently from coronary occlusions. This clinical improvement paralleled closely the lowered basal metabolic rate which likewise seemed to follow in line with the results obtained surgically from removal of the thyroid gland. As a result, Raab feels that thiouracil has a heart-protecting effect in that it suppresses the formation of thyroxin, thus likewise diminishing the sensitivity of the heart muscle to the action of adrenalin. The authors have

had no experience whatsoever in this type of case but feel that this work is certainly of great interest and should prove promising.

### Hyperparathyroidism

Since the discovery in 1925 by Collip that an extract of parathyroid tissue, namely parathormone, exhibited an extremely powerful effect on metabolism, much study regarding this unusual metabolic state has developed. It was in the same year, 1925, that Mandl in Vienna first treated von Recklinghausen's disease of the bone by removing a parathyroid tumor. The effect of hyperparathyroidism is decalcification found in man in a state known as osteitis fibrosa cystica. Because osteitis fibrosa cystica is rather an unusual clinical entity and consequently fairly uncommon in occurrence, it has as a result been assumed by many that a state of hyperparathyroidism is likewise equally rare. Keating and Cook<sup>16</sup> have reported a series of twenty-four cases collected by them in a period of two and one-half years at the Mayo Clinic and feel that hyperparathyroidism is not as uncommon as previously thought, but that the incidence has been thought small due to the fact that diagnosis has not always been made in the early cases as the early symptomatology they found to be notoriously vague and seldom pathognomonic. They cite the work of Albright and his associates at the Massachusetts General Hospital, who in 1934 reported seventeen cases and after careful analysis of these cases come to the following conclusions:

1. Hyperparathyroidism can occur without any evident bone disease.

2. The urinary tract is involved more often and a more common manifestation of hyperparathyroidism than skeletal involvement.

3. Hyperparathyroidism is relatively common.

4. In the formation of renal calculi it is a definite etiological factor.

Since this work of Albright (1934), which was a milestone in our present-day conception of this condition, much study has been given this condition and just three years ago Cope (1942) reported sixty-seven cases collected from the Massachusetts General Hospital over a period of ten years, which again proves its incidence to be anything but rare. The present study of Keating and Cook includes cases observed and studied over a two and one-half year period from September, 1942, to January, 1945, during which time hyperparathyroidism had been proven at operation. This apparent increase in incidence is obviously due to careful study, particularly to patients having renal calculi. They divided this series of patients into three groups: (1) Those showing the classic picture of osteitis fibrosa cystica; (2) those showing minimal or atypical demineralization of the skeleton, or those patients having had, or had at the time, renal calculi; (3) those cases in which there were renal calculi but no evidence whatsoever of skeletal involvement after careful roentgenographic examination. The average age at time of operation was found to be 44.5 years and there were fourteen men and ten women in the series, thus somewhat contradicting the earlier conception that women outnumbered men by a four-to-one ratio.

The symptoms, by and large, were divided into three groups, namely: (1) Those resulting from the altered chemical changes in the blood and urine; (2) those resulting from the involvement of the skeleton; (3) those resulting from involvement of the urinary tract.

The symptoms resulting from the chemical changes consist of pronounced

muscular atony, weakness, fatigue, constipation, anorexia, weight loss, and occasional nausea and vomiting. The chemical changes are actually very characteristic. There is an increase of blood calcium which may rise as high as 20 mg. or more per 100 cc. of blood and with this there is a reduction of inorganic phosphorus in the serum. It should be remembered, however, that should the excretion of calcium by the kidney keep pace with the increased mobilization from the bones, a normal blood calcium level would be found which would conceivably mislead one in making a diagnosis. In the normal individual the blood phosphorus level is about 3 mg. per 100 cc. However, in hyperparathyroidism it may be decreased to between 1 and 1.5 mg. per 100 cc. There is likewise an increase in the plasma phosphatase and the urine contains excessive amounts of calcium so that a negative calcium balance usually results. In examining the urine, it is found also that phosphorus excretion is likewise increased.

Polyuria can at times be excessive and is often accompanied by polydipsia, this being due, of course, to the excessive excretion of calcium and phosphorus. It was pointed out by Keating and Cook that this polyuria and polydipsia have at times suggested an erroneous diagnosis of diabetes insipidus as was the case in their series. Polyuria and polydipsia were marked in eleven cases or 46 per cent, showing them to be fairly common clinical findings. Interestingly enough, also, they found that in sixteen cases or 67 per cent, the urine's specific gravity never exceeded 1.015, which they interpreted to be the result of either a hypercalcinuria or evidence of impaired renal function.

**Symptoms Referable to the Urinary Tract**—It has long been thought and again pointed out by Keating and

Cook that excessive excretion of phosphorus and calcium in the urine favors the formation of renal calculi and even calcification of the renal tubules. Thus, the urinary symptomatology produced in hyperparathyroidism can be due either to urinary calculi, infection of the urinary tract resulting from renal calculi and impaired urinary function resulting from nephrocalcinosis. In eighteen of the twenty-four cases studied by them, symptoms were directly or indirectly attributed to renal calculi. Multiple calculi bilaterally occurred in fourteen of the twenty-four cases. Fourteen of the patients also had previously been operated on, some more than once for renal calculi.

**Symptoms Referable to the Skeleton**—These symptoms vary considerably from vague pains and aches to pathologic fractures, bone cysts, and bone deformity.

**Diagnosis**—This is essentially a laboratory diagnosis and depends on (1) an increase of calcium in the blood serum; (2) a lowered blood phosphorus level; (3) hypercalcinuria; (4) roentgenologic evidence which may vary from demineralization to the classic findings of osteitis fibrosa cystica.

As noted before, the normal blood calcium level in the blood is approximately 10 mg. per 100 cc. and the authors point out that although the blood calcium is usually increased, it does not always necessarily have to be; particularly if there is a concomitant hypercalcinuria. The average phosphorus level in their series was not markedly reduced, again some showing within normal limits, although in many cases they felt that the depression of phosphorus was the best clue to diagnosis, especially with an equivocal calcium level. Increase in the phosphatase is not pathognomonic for hyperparathyroidism and it was well pointed out by them that this is an indication of

bone disease in general and oftentimes an increased level of the phosphatase remains long after operation when the serum phosphorus and urinary calcium excretion had long since returned to normal levels. Roentgenologic examinations vary considerably in degree in the cases they studied, the classic findings or osteitis fibrosa cystica being present in seven cases of the twenty-four. Nine cases or 38 per cent showed minimal or atypical demineralization of the skeleton, but the changes were not sufficiently pathognomonic to make a diagnosis.

One of the most interesting conclusions derived from this study was the fact that in twenty-two of the twenty-four cases, or 92 per cent, there was calcification of the kidneys or renal calculi and in eighteen cases, or 75 per cent, the chief clue to diagnosis was due to renal calculi and the authors again emphasize the fact that (1) hyperparathyroidism is more common than generally accepted; (2) that renal involvement is not only more common but more important diagnostically than skeletal involvement, and (3) in any case of renal calculi, hyperparathyroidism should be suspected until proven otherwise.

### The Skin in Diabetes

To date, it has been felt generally that there were no specific skin lesions unique to the diabetic, although there have been certain types of skin lesions which occur quite frequently in the diabetic. These frequent skin findings, of course, have consisted of carbuncles, associated skin changes with persistent pruritus vulva, xanthosis, xanthoma diabeticorum, and the lesions described originally by Oppenheim, known as necrobiosis lipoidica diabeticorum. The most frequent skin condition in the average diabetic encountered has been epidermophytosis, commonly known as athlete's foot, of which

the appearance and clinical manifestations are only too well known. The importance of this latter condition cannot be overemphasized as it so often leads to serious complications. It has been our impression that this condition, although not in any sense limited to the diabetic, is certainly more frequently found in the diabetic than in the average nondiabetic.

An entirely new type of skin lesion known as skin diabetes has been reported during the past year by Urbach.<sup>17</sup> He describes a condition characterized by hyperglycodermia without hyperglycemia. Utilizing a microchemical technic and the electric punch biopsy method, he has been able to measure quantitatively the amount of sugar in the skin, and finds it to be between 58 and 68 mg. per 100 gm. A ratio in excess of 70 per cent between the skin content and the blood sugar content, he feels, is pathognomonic in diagnosing this condition which he has designated "independent cutaneous glycohistechnia."

The interesting aspect of this paper from a practical point of view is that he has found, in handling cases resistant to the usual dermatologic treatment of furunculosis, eczema, pruritus, etc., that the use of a diabetic diet and sometimes small divided doses of insulin are often of value in treatment. As yet, this work has not been confirmed and it will be of great interest to check the results of further investigation on this subject. Perhaps the beneficial effect of insulin at times in the vagotonic nondiabetic individual might be possibly comparable to the reported beneficial effects of insulin in the skin lesions.

### Obesity

This is undoubtedly one of the commonest ailments to which the flesh falls heir. Its importance is not only from the



many disadvantages it causes itself but also its concomitant association with other disease states, the most frequently encountered being diabetes mellitus. When one considers the dietary habits in this country, it is amazing not how many obese people are found, but why more people are not obese. Some thirty-five years ago, Van Noorden estimated that an excess of 200 calories per day over the necessary requirement would in the course of a year lead to a gain in weight of approximately twenty-four pounds in the average individual.

During the past twelve months, several investigators have again studied the subject both from the aspect of uncomplicated obesity and also obesity associated with diabetes mellitus and all agree that the medical profession as a whole has been lax in the management and consequent weight reduction of the obese patient, particularly the obese diabetic. This was particularly stressed by Hamff.<sup>18</sup>

**Etiology**—The fundamental cause of obesity is the disproportion between the caloric intake and the expenditure of calories, thus creating a positive energy balance. Nature oftentimes helps the body to regulate a constant weight in that the appetite adjusts the caloric intake to the extent that it does not exceed the actual physiological needs. It is for this reason that attempts with certain drugs have been made to promote appetite depression. As will be discussed later, the recent work of Pelner<sup>19</sup> has been directed along these lines.

For years obesity has been divided into two general types, namely, the exogenous and the endogenous. In the exogenous type, the caloric intake is far in excess of the body requirements and thus fat is stored in the body which, if allowed to continue, will cause obesity. For obvious reasons, treatment in this type

should not be too difficult. In the latter type (endogenous), there is a drop in the rate of body oxidation resulting from dysfunction or imbalance of one or more of the endocrine glands, striking examples of this type being the myxedematous state, Cushing's syndrome, and the obesity seen in Fröhlich's syndrome where the basic disturbance would appear to be traceable to the pituitary gland.

**Management**—As pointed out previously, diet is still the basic principle in the treatment. Hamff suggests an 800-calorie diet consisting of carbohydrates, 75 gm., proteins, 70 gm., and fat, 25 gm. He further emphasizes the importance of giving supplemental vitamins to compensate for the deficiency present in any of these reducing diets. Such a diet as this or one suggested by Evans years ago, consisting of a low carbohydrate, high protein, and no extra fat intake, is satisfactory. Danowski and Winkler<sup>20</sup> feel reeducation in basic eating habits essential for permanent reduction, that a daily negative caloric balance is of secondary importance.

Control of hunger is undoubtedly one of the most difficult problems confronting the obese patient on a reducing diet. For appetite depression, Pelner advocates the use of *benzedrine sulfate* and *atropine sulfate* in gradually increasing doses. He feels that the doses have to be gradually increased every two or three weeks to prevent any relative tolerance which may develop and prevent gradual weight loss. The dosages employed were initial doses of benzedrine sulfate, 5 mg. three times a day, increasing gradually over a period of weeks to 10 mg. three times a day. This was combined with atropine sulfate, 0.08 mg. ( $\frac{1}{750}$  grain), increasing to 0.24 mg. ( $\frac{1}{250}$  grain) three times a day. Pelner gave these drugs one hour before each meal together in a capsule.

Hutton<sup>21</sup> feels that the use of thyroid and injections of from 0.5 cc. to 1 cc. of anterior pituitary substance twice a week is of distinct value, particularly in the endogenous type. Kalb<sup>22</sup> studied the effects of massage in the treatment of obesity and came to some very interesting conclusions. In a series of sixty cases, forty were placed on a low caloric diet and in addition received massage on one limb twice a week. The other twenty patients were put on no diet but given massage alone. The forty patients treated with diet and massage to one limb lost weight and showed a decrease in the circumference of both of the limbs, massaged and not massaged. The twenty patients receiving body massage but on no diet did not lose any appreciable weight and there was no decrease in circumference of the limb so massaged with the usual vibrating machine. As a result of this study, Kalb has very definitely exposed the fallacy of this popular massage treatment of obesity.

The authors still are very definite in the opinion that diet is the basic therapeutic measure in the treatment of obesity. Drugs such as *benzedrine*, *dexadrine*, *tincture of belladonna*, and such are certainly of help in controlling hunger. The use of *thyroid*, *proloid*, *pituitary* substances and the like should

be limited to endogenous types of obesity and then used only after careful study with proper indications.

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## PHYSICAL MEDICINE

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### Methods of Crutch Management

Deaver and Brown<sup>1</sup> state that the modern crutch walker can become efficient on crutches if he is willing to follow a program, step by step, under the direction of the instructor, amassing simple knowledge, using common sense in the application of that knowledge, and

persisting unrelentingly in regular practice.

Since it is not always evident at once how long a pair of crutches should be and just where the hand bars should be, it is wise to begin with a pair of extension crutches. An extension crutch consists of two vertical uprights and one

vertical piece containing a series of holes which is inserted between the two vertical uprights and adjusted by means of bolts and screws. The hand pieces can also be changed, since there are holes in the vertical uprights with bolts and screws for adjustment.

Each shoulder crosspiece should have a rubber cover over it, since paralysis may result if the subject leans too heavily on the hard wooden surfaces of the crutches.

In order to assume the proper crutch position, the subject should take the weight of the body on the hands and not on the shoulders.

A rubber tip should always cover the base of each crutch to discourage slipping of the crutch and fear on the part of the subject.

In adjusting crutches, the height of the crutches and the level of the hand bars are primary considerations. If crutches are too long, they force the shoulders up and the subject has no way of pushing his body off the floor. If crutches are too short, the subject leans over too far and stands poorly. The height of the crutches and the level of the handpieces depend on the extent of the disability, the strength of the muscles needed for crutch walking, the amount of weight the crutches must carry, the crutch gait selected, and the skill of the subject in manipulating the crutches.

A large dealer has figured out a shortcut method which should be of considerable assistance to hospital executives and physicians, either in fitting crutches from stock or in ordering crutches for special cases. This dealer has taken an average of patients' height and the average length of crutches used for a large number of cases and finds that the proportion between a man's height and the length of crutches suitable for him is

77 to 100. In other words, given the height of a patient, the proper length of crutches will probably be 77 per cent of the height.

The method Deaver and Brown use is to help the subject to stand up against a wall as straight and as tall as he can, with shoulder girdle relaxed and not raised, upper extremities relaxed and at sides and heels against the baseboard. He may have to be supported. If the subject cannot stand up against the wall for measurement, he should lie down on his back and the measurements should be made with just as much care, especially with regard to the position of the shoulder girdle and upper extremities.

The procedure is to measure the distance from the armpits to the floor. This measurement must be considered to include the rubber tops of the crutches as well as the rubber bottoms. Since shoulder crosspieces are not straight across but slightly concave to fit the armpit, the measurement must be thought of as extending from the center of the shoulder crosspiece.

If an error is made, it is much better for the subject to start with crutches which seem a little low than to start with ones that are too high, even if the extra height is only an inch.

Walking with crutches involves:

1. Standing as erect as possible by holding a crutch under each arm.
2. Grasping the crosspieces with fingers and thumbs.
3. Straightening the elbows to allow the hands to support most of the weight of the body.
4. Moving the crutches forward as needed.
5. At least one straight knee, braced or fixed by artificial or surgical fusion, to maintain the weight of all or part of the body erect during progression.

Preparation for crutch walking includes (1) a muscle test to discover the extent of muscular weakness; (2) an exercise program to develop strength in the muscle groups necessary for crutch walking, and (3) instruction in how to stand and balance with crutches before taking any steps.

Everyone has experienced the weakness and insecurity of balance which follow even a few days in bed. When a subject is confined to bed or wheel chair, his muscles immediately start becoming weaker and smaller, and it is only a matter of days before he notices, with the greatest chagrin, the weakness and flabbiness which result from disuse.

In view of this weakness and flabbiness which inevitably follow inactivity, it is a mistake to instruct the subject who has been bedridden suddenly to stand erect and walk without reconditioning the muscle groups needed for standing and walking.

Generally speaking, if a subject is in bed because of a condition which will not produce an orthopedic disability, he should exercise as soon as his condition permits whether his period of confinement to bed is expected to be of short or of long duration. A group of exercises should be carefully worked out on the basis of what the condition will or will not allow.

For those who will use crutches, it is good medical practice to prescribe an exercise program for the specific muscle groups used in crutch walking.

All crutch walkers should learn at least two gaits: A fast one, to be used in the open for making speed, as is needed in crossing a street; and a slow one for crowded places, where space is limited but balance must be kept as slow progression is made.

**Standard Crutch Gaits—*Four-Point Alternate Crutch Gait***—Crutch-

foot sequence: (1) Right crutch; (2) left foot; (3) left crutch; (4) right foot.

The four-point alternate is the most elementary standard crutch gait and consists in advancing one crutch, then the opposite foot, then the other crutch, then the opposite foot, then the other crutch and finally the other foot. At all times there are three points of support on the floor while one crutch is in the air.

***Two-Point Alternate Crutch Gait***—Crutch-foot sequence: (1) Right crutch and left foot simultaneously; (2) left crutch and right foot simultaneously.

This is no more than a speeding up of the four-point alternate gait. This is a faster gait than the four-point; in fact, there are persons using this gait who can walk as fast as an average normal walker making good speed.

***Three-Point Crutch Gait***—Crutch-foot sequence: (1) Both crutches and the weaker lower extremity; (2) the stronger lower extremity.

The three-point crutch gait is the one in which the two crutches and the weaker limb are placed on the floor simultaneously, then the stronger limb, which, being strong enough to support the weight of the body, needs no crutches. This gait is used by those having one lower extremity which cannot take full weight-bearing and one which can support the whole body weight.

***Tripod Alternate Crutch Gait***—Crutch-foot sequence: (1) Right crutch; (2) left crutch; (3) drag body.

If the crutches are placed apart and slanted well forward at their lower ends, they form the two anterior points of a tripod, while the third and posterior part of the tripod is formed by the body of the patient inclined forward at its upper part, with the feet well behind.

The one essential in bad cases is that the tripod should have a large base, and the body be sufficiently inclined forward

to keep the center of gravity in front of the hips.

**Tripod Simultaneous Crutch Gait** — Crutch-foot sequence: (1) Both crutches; (2) drag body.

The tripod simultaneous gait differs from the tripod alternate gait in that the two crutches are placed on the floor at once. The body is jerked, dragged, or slid along the floor.

The Air Surgeon of the Army, in collaboration with the Institute for Crippled and Disabled, New York, where Dr. Deaver is medical director, has prepared a booklet, "Let's Walk."<sup>2</sup> This gives the following exercises:

**Preparing the Triceps** — From a hand-on-chest position, extend arms forward, sideward, and upward. Try to touch the ceiling and the walls.

Though you may be in a full-body cast, push yourself up as far as possible. Tense upper arms.

- If you are in a leg cast, push yourself into a sitting position. Tilt body backward slightly with palms beside and behind you. Stiffen arms. Relax. As strength returns, put a box or book under each hand to give you some altitude.

Exercise the triceps while sitting on side of bed or in wheel chair. Grasp mattress or chair arm firmly, stiffen arms, and lift body upward as far as possible.

**Preparing the Finger Flexors** — Spread fingers wide and practice tightening the fists.

Stretch out on your back. Raise arms up and grab top bed rail. Tighten fists and squeeze.

A sandbox is a handy gadget. Tightly grab a handful of sand and then let it filter through your fingers.

Create finger power by squeezing a tennis or hard rubber ball. It's an old prize fighter's trick and very helpful. Give each hand equal time.

**Preparing the Quadriceps** — While in lying position, tense thigh muscles of strongest leg.

After raising your knee, straighten leg as stiffly as possible. Hold it a minute before resuming original position.

Sit on the side of your bed and raise the leg until it is straight out in front of you. Be certain the knee cap is tight. Relax. Bring leg down.

Another way to tone up the quadriceps: Put some sand in a bucket, hang the bucket over your ankle, and lift. Add more sand each day.

**Preparing the Abdominals** — If you are in a body cast, raise head and shoulders off the pillow for at least 8 inches.

Assume the horizontal position. Set palms on thighs. As you slowly elevate your trunk, start "walking your fingers" towards your knees.

On your back again. Clasp hands behind head. Lift torso off the bed about 10 inches.

Bring both legs up straight and close together, lower back flat.

Turn torso to left and grasp left bed rail with right hand. Turn torso to the right and grasp right rail with left hand.

**Crutch Walking Don'ts** — Certain practices must be avoided for good crutch walking. Remember these and prevent accidents:

Don't carry your weight on armpit rests; let the hands and hand grips take care of this. The armpit rest is to balance the upper part of the crutch under your arm. Pressure under the armpits can cause damage to nerves and may result in crutch paralysis, the most common of which is wrist drop. Don't hunch shoulders.

Don't overpad armpit rest; there is no need for this since the rests should not carry your weight.

Don't have crutches too long. Correct length prevents too great a spreading of

the props and preserves balance. Don't swing the crutches out; move them straight ahead.

Don't take too long a step. You may lose balance and fall.

If tips are worn, exposing wood, get replacements quickly.

Don't turn your feet out. Keep them straight—and go forward. Don't use crutches or canes without rubber tips. You may topple over.

### Low-Back Pain

**Functional Decompensation —** Hauser<sup>3</sup> states that low-back pain is frequently due to an imbalance between the demand made on the back and the capacity of the back to do the work required of it. In addition to the symptoms of low-back pain, fatigue, soreness, and stiffness in the back, the decompensated back has an altered posture. The normal dorsal and lumbar curves are increased. The lumbosacral angle is more acute, increasing the shearing force. The body sags, putting strain at the lumbosacral and sacroiliac joints, with the resulting inflammation of these joints.

A cast can be applied to correct the position, decrease the strain on the lumbosacral and sacroiliac joints, and increase the capacity of the back.

#### Application of Cast

- A. Forward bending of body at hips.
  1. Lumbar curve straightens.
- B. Extension.
  1. Lengthens body and decreases curve.
- C. Cast fixes pelvis and lumbar spine.
- D. Body always assumes upright position (self-righting reflex of Sherrington).
- E. Corrected lumbar curve fixed. Self-righting reflex converts cast into an active corrective force against the dorsal kyphosis.
- F. Power in muscles of abdomen and back developed through maintaining upright position in corrective cast.
- G. Weight is transmitted through cast from dorsal spine to pelvis. Strain

released on lumbosacral and sacroiliac articulations. Permits inflammation to subside.

After full benefit from the plaster brace has been attained, the patients are advised to avoid strain from lifting, standing, or sitting and to arrange for rest periods during the day; instructions are given in corrective and restorative exercises. For particular cases, heat, traction, analgesics, or other specific treatment is prescribed.

### EXERCISES

#### FIRST SERIES

*Principle:* That exercises be in accord with normal function of back, which is to maintain the erect position.

Each exercise must start and end with correct standing position.

Full inspiration is advised at beginning of each exercise. Expiration upon completion of exercise.

Raise arms—anteriorly—overhead and lower.

Raise arms—laterally—overhead and lower.

Bend trunk to right at waist and return—repeat to left.

Bend trunk forward at hips, maintain extended position of back and head, return.

Raise leg extended optimum distance and rhythm, maintaining erect position; repeat to the right, left, forward, sideward, backward.

#### SECOND SERIES

Examples of exercises suggested for developing strength.

Lie on back, arms folded on chest, come to a sitting position.

A. Lie on back, raise one leg and lower; repeat with other leg.

B. Raise both legs and lower, back must be held flat throughout exercises A and B.

Push-up—keep abdomen firm and back straight.

#### THIRD SERIES

Physiological Exercises.

Normal gait: Body held erect. Propulsion carried out by heel-toe gait. A properly fitted shoe with low, broad heel, flexible shank, and Hauser bar is worn.

The etiology of a functional decompensation of the back would be dependent on all factors that increase the load or decrease the strength. Since the normal function of the back is to hold the upright position, prolonged sitting or prolonged standing would be the most common way to increase the load. Debilitating diseases would cause a decrease in capacity. Poor hygienic conditions, lack of exercise, insufficient fresh air, and sunshine, and inadequate diet would also be contributing factors to a functional decompensation. The combination of an increased load with decrease in strength would tend to make the decompensation come about more rapidly and cause it to be more severe. The most usual cause in Hauser's experience is long sitting and long standing in individuals who have poor muscle tone due to lack of proper exercise. They get insufficient rest so that the muscles are always tired, and they get inadequate exercise to keep up their strength. Since this is a fatigue condition, anything that would cause fatigue would be a factor. A frequent cause of fatigue in people with low-back pain is nervous fatigue. The constant worry and insomnia associated with nervous strain increase the fatigue and contribute toward the decompensation.

In the consideration of low-back pain from the standpoint of the general surgeon, Moore<sup>4</sup> stresses the following points: For acute lumbosacral strain, the *recumbent position* usually gives relief, lying on the back or the sound side of the body and *thighs* slightly *flexed*, a *pillow* between the *knees*, and some form of *heat* to the affected part. Add to this a firm mattress and you have good treatment. The referred pain in the leg will disappear as the back improves. They should be kept in bed as long as movement causes pain.

On arising, they will be more comfortable with a tight binder and should continue heat in some form. Later, stooping and bending *exercises* just short of inducing pain are encouraged. The majority of these cases show no roentgenographic evidences of injury.

For postural lumbosacral strains, local heat gives patients most relief. The pendulous or relaxed abdominal wall should wear an abdominal support. Other postural corrections should be referred to the orthopedist.

With facet syndrome, sudden pain in the lumbosacral back may be due to a slight subluxation of one or both inferior articulating processes of the fifth lumbar vertebra. These respond amazingly to *manipulative measures*. The procedures recommended are given in detail.

Patient lies flat on his back on a firm table and braces himself by holding the sides of the table. The operator, standing at the foot of the table, flexes the patient's hip and knee joints while grasping the ankle. The patient is then asked to give a violent kick, at which time the physician pulls strongly on the ankle in the line of the body. If properly synchronized, the maximum force is obtained when the leg is in full extension. Five to ten kicks may be required, depending on the amount of relief from pain and freedom of hip flexion. The kicking and pulling produce a forward thrust of the sacrum on the fifth lumbar vertebra in the opposite direction to which the slipping has occurred. Heat and rest for a few days complete the treatment with admonition to avoid movements that cause pain. After two to four weeks, stooping and bending exercises are recommended.

For sacroiliac strain, rest on a firm mattress, some form of heat, and a sacral compression is good treatment. Patients are likely to be more comfort-

able on the back with a pillow under and between the knees. Patients are allowed up when the upright position does not cause pain. A firm binder or belt around the pelvic girdle affords some comfort. They should continue with intermittent use of heat. The recommendations for stooping and bending exercises are the same as in lumbosacral strains.

Contracture of the fascia lata has been suggested as a common cause of low-back pain.

A high percentage of relief is reported by simple division of the iliotibial band above the great trochanter.

For lumbago, the treatment is heat, massage, and early activity.

**Backache in Soldiers**—According to Fox,<sup>5</sup> during the past two years the orthopedic and the psychiatric sections of a general hospital have collaborated to an increasing extent in the attempt accurately to evaluate and appropriately to treat soldiers complaining of backache. The orthopedists were early aware of the fact that the quality of the patient's desire for recovery was often a more important factor in determining his return to effective duty than the extent of the actual organic changes in his spine as demonstrated by roentgenographic examinations. The degree of incapacity was often considered to be out of proportion to the actual orthopedic findings and the psychiatrist endeavored to consider the patient's complaints in the light of his personal attitudes, especially as they affected his service in the Army. Although a few of the patients made the most of their symptoms for personal reasons, out-and-out malingering was rare and even the well-known hysterical "soldier's back" was encountered infrequently. Nearly all of the patients were returned to duty and such follow-up information as is available indicated that most of them remained on a duty state

after returning to their units. The orthopedist in charge of the patients with back complaints concluded that in more than half of the men personal factors were of greater significance in the production of the disability than whatever orthopedic findings could be demonstrated. During the past few months all of his patients complaining of backache have been referred for psychiatric consultation.

The orthopedist in charge of the patients with backache in an Army General Hospital overseas requested a psychiatric consultation on every man admitted to his service over a period of several months. After the orthopedic and psychiatric observations had been recorded, an approximate evaluation was made of the relative importance of these factors in each case, and at the same time the relative prominence of these factors as they appeared in any one patient was compared to what was encountered generally among the entire group of patients under consideration. The patients were divided into three groups, depending upon the severity of the factors present. Almost all of the patients (constituting the first two groups) were returned to duty as improved. All of the patients who were returned to duty had been given several weeks of *postural treatment*—an active type of physiotherapy which was carried out by trained physiotherapists.

The value of this type of treatment in the improvement of personal attitude as well as posture is discussed in connection with case illustrations from the various groups. The embryologic development of the erect posture is indicated and the intimate association in early childhood of the struggle toward independence and the attainment of the capacity to stand and walk is stressed. This is followed by illustrations from colloquial language



showing that the adult retains a sense of the symbolic importance of posture.

Further cooperation between orthopedists, psychiatrists, and physiotherapists is urged for the successful treatment of soldiers with backache.

### Rhizomelic Spondylosis

Rhizomelic spondylosis (Marie-Strümpell arthritis), as the name implies, is a disease of the spine and root joints. Baker<sup>6</sup> states that experience has shown that atrophic arthritis does not respond

carry out the physical therapy, it was necessary to develop apparatus to help correct deformities, to help maintain the correction, and to prevent unnecessary discomfort to the patient during the treatment. If any real benefit is to be derived from physical therapy measures, the patient must be relaxed and comfortable during the treatment. The patient with Marie-Strümpell arthritis usually has fixed deformities and is difficult to handle on the ordinary treatment table, especially when in the prone position.

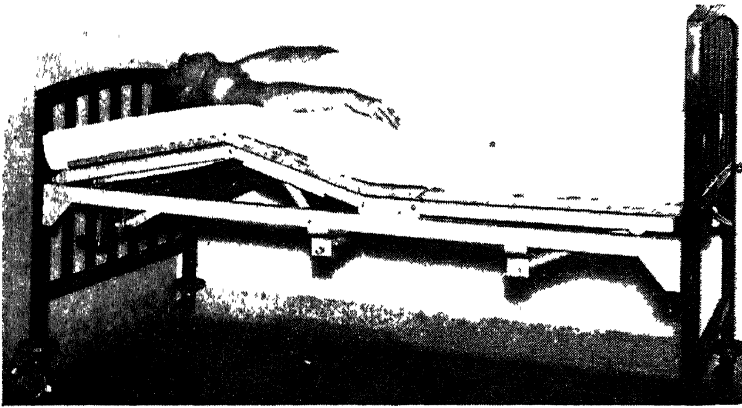


Fig. 1—A gatch bed with a latex mattress and a fracture board. The fracture board is hinged to conform to the adjustable bed, and hyperextension of the spine is obtained by placing the patient's head toward the foot of the bed. (Baker, I. D.: Arch. Phys. Med. 26: 391 (July) 1945.)

to roentgen therapy. The fact that rhizomelic spondylosis does respond to small doses of ray therapy is at least indicative that the cellular changes in this disease are of different nature from those in atrophic arthritis.

As a rule, no corrective measures are attempted until all studies are completed and roentgen therapy has been given. The ray therapy gives early alleviation of pain with relief of muscle spasm and allows more rapid and less painful correction of the deformities. On relief of symptoms or after completion of one series of roentgen ray treatments, corrective measures are started and physical therapy measures are begun. To

It was found that an operating table head rest, which is adjustable in all directions and which has attached shoulder supports, could be used to advantage in overcoming this difficulty. (A baseball catcher's mitt makes a fairly satisfactory substitute for the head rest. With the baseball mitt, sandbags are used to support the shoulders.)

To add to the patient's comfort when he is in a supine position and to aid in correcting deformities, a hinged fracture board similar to that shown in Fig. 1 was prepared to fit the treatment table.

Fig. 2 shows exercise equipment which was designed to aid in the correc-

tion of contractures in the anterior portion of the shoulder girdle, the thoracic cage, and the abdominal wall and to help in developing the posterior shoulder girdle muscles and the thoracic bundles of the sacrospinalis muscle. In using

which the hyperextension forces act to correct the flexion deformity of the spine and to increase the excursion of the thoracic cage.

Swaim outlined the orthopedic treatment of ankylosing spondylitis and re-

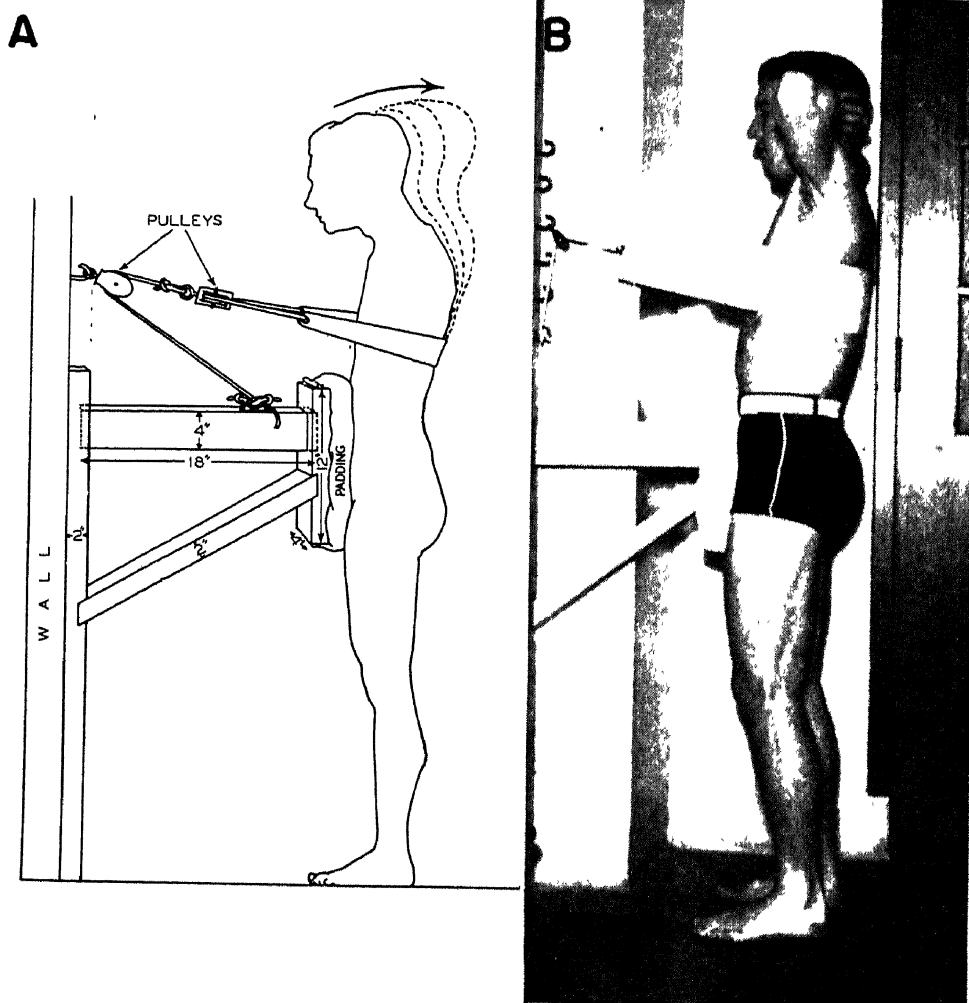


Fig. 2—*A*, An exercise apparatus designed to prevent hyperextension in the lumbosacral area; to aid in the correction of contractures in the anterior portion of the shoulder girdle, the thoracic cage and the abdominal wall during correction of the dorsal curve, and development of the thoracic bundles of the sacrospinalis muscle and the posterior muscles of the shoulder girdle. *B*, Use of the exercise machine. Note that the patient's pelvis is fixed by the gluteal, hamstring and low abdominal muscles and is held snugly against the wall pad. (Baker, I. D.: *Arch. Phys. Med.* 26: 392 (July) 1945.)

the apparatus, the patient stands against the wall pad and fixes the pelvis with the gluteal and lower abdominal muscle. The body strap is fitted snugly across the back and acts as a fulcrum over

ported the end results in 106 cases. He pointed out the necessity of maintaining correction of the deformities with some form of support. As a substitute, a brace was developed.

As the statistics show, the best results are obtained in the early stage of the disease. Experience with the combined therapy indicated that better results are obtained if the patient is hospitalized until full correction of the deformities is obtained and early signs of return of normal muscle power have appeared. Repeated hospitalization at three- to six-month intervals serves to stimulate the patient's interest in his home therapy and has been of benefit in morale building, which is so necessary for patients with this type of chronic disease.

From some of the follow-up roentgen ray studies, it appears that the therapy has had a deterrent effect on the disease, in that there are signs of revascularization and retrabeculation in the subchondral areas about the sacroiliac joints in patients treated during the early stage of the disease. Repeated determinations of the sedimentation rate, when carried out, have shown a consistent return toward the normal. Certainly the combined therapy has been of great help in rehabilitating victims of this obstinate and difficult disease.

**Physical Therapy—Heat:** Diathermy, infrared ray treatment or use of wet compresses.

Massage and passive exercise to obtain relaxation and release contractures.

Active exercise to relax anterior part of shoulder girdle, thoracic cage, and abdominal and hip flexor muscles, and to develop posterior part of shoulder girdle and sacrospinalis muscles.

Swimming with effort at arching back. Deep-breathing exercise.

Postural training.

Treatments given twice each day.

**Rationale:** Relieve muscle spasm. Correct deformities and develop weak muscles to maintain corrections. Increase vital capacity. Improve posture.

**Parietal Neuralgia—McDonald<sup>7</sup>** states that parietal neuralgia is induced in the great majority of cases by some pathologic process or by pressure on the

spinal nerve root, usually at the point where it emerges from the intervertebral foramen. The commonest cause in older patients is undoubtedly a hypertrophic arthritic process of gradual encroachment on the foramen. In younger patients the question of postural strains must be considered. Structural scolioses, injuries and tumors of the bone may be readily recognized, but functional scoliosis may escape notice. This will only be seen by careful examination of the patient's back and posture. Any complete physical examination must include careful observation of the patient's back, preferably with the patient standing in his bare feet.

Treatment of parietal neuralgia depends upon the process which has caused it. In the arthritic patient, the use of *heat* and *massage* over the affected area will be of value. Limitation of the movement of the spine by adequate braces may be useful and *roentgen therapy* to the spine has apparently been beneficial. Avoidance of prolonged walking and standing and a period of recumbency in a firm bed may be useful from a therapeutic viewpoint and also as an aid in diagnosis. In younger persons, especially those of asthenic type, the use of graduated postural *exercises* is of chief importance. By their use, muscular tone is improved, and ligamentous strain is relieved. Marked improvement of peripheral circulation is frequently seen in association with deep-breathing exercises, and an improved position and circulation of the abdominal viscera often alleviate the indefinite gastrointestinal symptoms of which these patients complain. A short lower extremity may be corrected with a lift in the heel sufficient to cause the pelvis to be level and to restore the symmetry of the spine, thus overcoming the mechanical basis for strain. Adequate rest is also beneficial.

**Shoulder Periarthritis**—The typical case of periarthritis, or frozen shoulder, according to Lippmann,<sup>8</sup> commences with a mild ache in the shoulder or arm, which grows inexorably worse and is accompanied by progressive stiffness. The pain grows in intensity, becoming almost insufferable, and the stiffness slowly increases to the point of almost complete scapulohumeral fixation. After months of growing distress (often increased by scalene spasm and pain down the arm), the pain starts to abate and shoulder motion begins to improve. Undulant progress continues until the shoulder is again clinically normal. During the period when the disease is progressing, the pain dominates the picture. In the period of improvement, stiffness is the most prominent complaint.

The typical clinical aspects of periarthritis, or frozen shoulder, shows that, though its duration is unpredictable, the condition almost invariably terminates spontaneously in complete recovery.

Surgical investigations on more than thirty cases of frozen shoulder have revealed that at least in most instances the subdeltoid bursa and underlying musculotendinous cuff are not involved and, instead, tenosynovitis of the long biceps tendon and sheath is consistently encountered.

Adhesive tenosynovitis extends from the sheath into the outer quadrant of the shoulder joint proper, but the entire inflammatory process subsides spontaneously when the tendon becomes firmly attached to the bicipital groove and its motion is so obliterated.

The pathologic sequence underlying periarthritis provides a guide for the administration of conservative therapy and suggests a simple surgical approach when more rapid cure is desired.

The pain and spasm seen in calcification of the tendon cuff of the shoulder,

Howorth<sup>9</sup> states, may be relieved in some cases, especially the acute ones of short duration, by any one of several treatments.

**Heat**, in the form of a lamp, hot-water bag, electric pad, or hot packs, may provide some relief. **Short- or long-wave diathermy** may relieve some shoulders, and may even be followed by absorption of the calcareous material in the early acute ones. However, an acute shoulder, with inflammation of the bursa, or tension in the tendon, is often made worse by heat.

**Cold** is usually more comforting than heat, especially in the very acute cases. Ice packs may be used, but **ethyl chloride spray**, as reported by Kraus, is usually more effective.

Massage of the bursal region is likely to increase the pain in most cases, though **gentle massage** of the adjacent muscles may be used to maintain muscle tone. Manipulations or stretching usually increases pain and spasm, and often does more harm than good.

**Exercises** are of great value, and are the most important of the various physical therapeutic measures.

The pendulum exercises are the simplest, easiest, and least painful; they should be done with the arm in flexion and hanging loosely, *i. e.*, with the trunk flexed, or with the subject lying prone upon a table with the arm over the side.

**Aspiration**, irrigation, or puncture of the calcified area may give relief, chiefly by the release of tension.

### Electric Muscle Stimulation

Experiments were carried out by Wehrmacher, Thomson, and Hines<sup>10</sup> on denervated gastrocnemius muscles of albino rats in order to determine the conditions under which electrical stimulation would most effectively retard atrophy. The results of this investi-

gation clearly indicate that the atrophy of muscle following denervation can be appreciably retarded by *electrical stimulation*. The effectiveness of the treatment appears to depend on the extent to which tension is developed by the muscles during their treatment. The duration of an effective period of treatment can be very short if the muscles are stimulated under conditions which permit the development of maximal isometric tension. The most important factor in treatment would appear to be the quantity of tension developed rather than the particular kind, frequency or phase pattern of the electrical stimuli. In some respects the retardation of atrophy by electrical stimulation suggests an analogy to the charging of a wet storage cell.

That electrical stimulation, resulting in a conservation of a large mass of functional tissue is supported by the findings that such muscles possess normal water contents and increased concentration of creatine, and are stronger than their untreated controls. However, such muscles are stronger because of their greater mass rather than because of any improvement in the functional capacity of the tissue itself. The results confirm those of Fischer in the observation that electrical treatments adequate to retard atrophy fail to check the gradual loss of strength per unit mass of tissue which occurs after denervation.

It is believed that these findings offer some suggestions for the selection of an effective regimen for the treatment of muscles after peripheral nerve injuries. In general, the most effective stimulus modality should be the one which causes the development of the greatest amount of tension by the muscles. The findings point out the futility of employing stimuli which elicit only feeble contractions and suggest that the effectiveness of the

treatments would be independent of the kind and frequency of the electrical stimuli employed, provided comparable amounts of tension were developed by the treated muscles. The muscles to be treated should be weighted or restrained in a manner which will allow the greatest amount of stretching permitted within physiologic limits. The total number of the stimuli can be small and the duration of the treatments can be brief. Nothing would appear to be gained by prolonging the treatments beyond a certain minimal duration. On the other hand, the prolongation of the periods of treatment to the point of causing a considerable degree of fatigue in the muscles appears not to be deleterious. The effectiveness would appear to depend on the frequency with which the treatments are given. It is obvious that all of these optimal conditions cannot be realized in any given therapeutic regimen. Some modifications must frequently be made for the comfort of the patient, but, when these are made, it can be anticipated that less effective retardation of atrophy will be found. It is believed that the investigators who have reported negative results with electrical stimulation either failed to employ stimuli of sufficient intensity or did not provide optimal stretch conditions for the development of maximal isometric tension.

Jackson and Seddon<sup>11</sup> state that for many years the rôle of electrical stimulation in the treatment of lower motor neuron lesions has been the subject of lively controversy; and since the beginning of the war interest in this form of treatment has been quickened by the occurrence of thousands of cases of peripheral nerve injury. The results of animal experiments and of observations in man, though at times conflicting, are now consistent enough to warrant the formulation of certain conclusions.

It has been proved experimentally that the wasting of denervated muscle—a process prejudicial to recovery—can be prevented to a considerable extent by regular electrical stimulation of the muscle with stimuli of long duration, such as are provided by a galvanic battery.

A fluid displacement method was used to measure the volumetric changes in the hand in cases of ulnar paralysis, some treated with, others without, galvanism. It was found that the application of ninety stimuli daily for six days a week was almost wholly effective in preventing wasting except during the weeks immediately following denervation, though even during this period such treatment reduced the rate of wasting. The stimuli were strong enough to produce a brisk contraction, and were given at the rate of thirty a minute, with an interval of one minute between each group of stimuli to permit recovery from any possible fatigue.

There was no evidence that electrical stimulation increased muscle volume, and hence it is important to start treatment as soon as possible, since whatever has been lost through delay cannot be regained.

There is no doubt that in ulnar paralysis daily galvanic stimulation is well worth while, and that the treatment should be continued until voluntary power returns. It is not yet known whether galvanism is equally effective in preventing wasting in large masses of muscle, since a tolerable stimulus does not affect all parts of a large muscle mass equally, the deep fibers tending to escape altogether.

**Bell's Palsy**—Pickerill and Pickerill<sup>12</sup> state that in Bell's palsy, it is said that 75 per cent of cases recover spontaneously, and therein the authors think lies the cause of lifelong disfigurement for many people. It seems to be always

hoped, sometimes presumed, that the particular case in hand is or will be one of the seventy-five, in spite of the fact that there is often no means of knowing if it will turn out to be so. Bell's palsy should rather be regarded from the point of view of those who do not recover spontaneously, and say that in 25 per cent of cases the present usual line of treatment results in complete failure and the patient is permanently disfigured; this is a more arresting point of view, and is likely to result in a considerable diminution of such failures. In every fresh case of Bell's palsy, the authors suggest that it should be assumed not that it will probably get well if little or nothing is done, but that it is possibly one of the twenty-five which will not recover by itself, and measures should be taken accordingly.

Probably the chief factor in nonrecovery of what should be the temporarily paralyzed muscles is their immediate and continued overstretching by the non-paralyzed muscles of the opposite side of the face. A common method of attempting to overcome this is by the use of a hook in the corner of the mouth attached by a loop to the ear; but, as will be shown, this is often worse than useless. A more simple and effective method of restraining the overaction of the muscles of the sound side is by means of strapping. It is applied thus:

*The Strapping Method*—The lower half of the paralyzed side is first smeared thinly with vaseline or oil. Two strips of half or three-quarter inch strapping are then applied to the clean sound side on a level with the upper and lower lips, starting about three-quarters of an inch in front of the ear. The sound side is pushed across to the paralyzed side, and while in this position the other ends of the strapping are firmly stuck down to the mastoid process on the paralyzed

side. Very adhesive rigid strapping must be used—not elastoplast. The strapping, once on, must be left indefinitely on the sound side. If it is removed, the skin becomes sore and there is difficulty in reapplying it firmly; moreover, the patient is discouraged from persisting with the treatment. When it gets soiled, another piece may be placed on top of it, and only in some real necessity should it be removed, gently, by the surgeon or nurse, with the aid of a solvent, and reapplied immediately. Nonadhesion to the paralyzed side is necessary in order to avoid the possibility of a pull on the paralyzed muscles and so that gentle massage may be given; also so that the patient may endeavor to make voluntary movements of the affected side in front of a mirror at the end of a week or ten days. The latter method is probably the most effective that can be employed to aid recovery, but it must be done while the normal side is out of action. That is to say, condition must be such that the only thing the paralyzed orbicularis oris or zygomatic muscles have to do is to respond, even if ever so feebly, to the will to contract; they must not be concerned also with opposing the pull of the muscles of the opposite side. The probable reason why massage and exercises are so often ineffective is that in the early stage of recovery the muscles are overpowered with work by having two jobs to do at once and, again becoming overstretched, anything gained is soon lost.

*Electrical Measures*—During the third week, if recovery is not obvious, the muscles may with advantage be stimulated with weak faradic currents. Minimal doses only should be used—just sufficient to cause visible contractions in the orbicularis and zygomatic muscles. The aim should be just to maintain tone and not to tire the muscle with violent

contractions. A current which causes any painful sensation is much too strong, and will do harm. The current should be tried first on the operator himself and then on the sound side of the patient before being applied to the paralyzed muscles. If a current which causes contraction on the patient's sound side causes no contraction on the paralyzed side, no attempt should be made to produce contraction by using a stronger current. Short daily treatments with very weak current should be ordered. The strapping should be kept on and above treatment continued indefinitely. It may be for only a week or two, but it may be for two or three months. The patient must be handled very strictly, and be impressed with the serious risk of taking the strapping off even for one occasion, no matter how seemingly important it may be.

### **Injuries of the Brain, Spinal Cord, and Peripheral Nerves**

Physical and mental rehabilitation of patients who have received a cranio-cerebral injury, according to Scarff,<sup>13</sup> requires good judgment and skill. The patient must be encouraged in every way to think that the injury has been only a slight one. Terms like "concussion of the brain" and "compound fractures of the skull" must be absolutely forbidden, and, in the presence of the patient, such simple terms as "bump on the head" and "cut on the head" substituted. Lumbar punctures in conscious patients are usually unnecessary and are particularly to be avoided. They add little useful knowledge, and have little therapeutic value, and leave a deep and bad psychological scar. An arbitrary period of bed rest for two to three weeks, as was formerly practiced, is no longer approved. Instead, as soon as the patient feels able to sit up or go to the lavatory, or to

have his meals, he should be allowed to do so. He should be encouraged to participate in the care of his room and his own person. **Physical therapy**, including passive motion, baking, massage, and electrical stimulation, should be directed to paralyzed limbs.

Recovery of function in extremities and sphincters after severe spinal injury may require weeks or even months. If meticulous care of the skin, bladder, and limbs, including massage, passive motion of joints, and corrective splinting, be maintained, many seemingly hopeless cases will recover a great measure of useful function.

**Peripheral Nerve Injuries**—Physical therapy should be instituted about the third week after suture. This should include daily massage, to improve circulation; passive and active motion to keep joints, tendons, and muscles supple; and galvanic stimulation, applied directly to individual denervated muscles, to preserve the contractility of muscle element and to prevent the atrophy of disuse. The minimum effective galvanic stimulation consists of thirty contractions of each paralyzed muscle, repeated three times daily, three days each week. More frequent stimulation is, of course, desirable.

Splints should be used as needed to reinforce weakened or paralyzed muscles and prevent contractures; but these splints should be of such a type as to allow free, voluntary, and passive movements of all joints. If plaster-of-paris splints are used, they should be worn only at night, and left off during the daytime, and the patients encouraged to carry out maximum passive and active movements during his waking hours.

### Rest

Pemberton,<sup>14</sup> in discussing the use of rest in convalescence, states that the

term rest should not connote mere inactivity in a physical sense; it is, rather, a phase of the physiologic life of a tissue, organ, or entity under which certain essential processes can occur, not only in regard to repair but also in regard to normal "living." This concept of rest is widely unappreciated by practitioners in general. The propriety or relevance of rest in a given disease bears no necessary relation to the absence of signs of fatigue, either subjective or objective. This point is of major importance, and ignorance of it explains some of the failures to utilize it constructively.

Rest is usually prescribed to an excessive or inadequate extent. One needs but to go to homes for incurables to see exemplified the physiologic consequences of uncritical bed rest. Perhaps the most conspicuous features of excessive inactivity have to do with circulatory inadequacies in both the blood vascular and the lymphatic systems, owing to loss of the accessory influences normally resulting from muscular contraction. Tissue edema, atrophic skin, and complete displacement of muscular tissue to some abnormal sites are common findings and illustrate extreme consequences of apparently minor deviations if they are allowed to persist.

More effective results would follow the prescription of rest if, instead of a blanket recommendation of rest, the prescription were made to specify the individual components which constitute it.

Conditioned rest is not negation of activity; as such, it could be harmful in many ways. In rheumatoid or atrophic arthritis, unconditioned rest may lead to ankylosis unless controlled. Conditioned rest in most cases should include some form of physical therapy, such as postural exercise.

Properly conditioned rest in bed: (a) Promotes passage of tissue fluids into



the vascular channels; (b) promotes opening of peripheral capillaries because of warmth induced by the bedclothes; (c) promotes relief from static strains incident to maintenance of erect posture; (d) promotes relaxation of the nervous system; (e) allows ptosed organs to assume proper position and function; (f) reduces the metabolic load, and (g) permits settlement of metabolic deficiencies. It should be added that faulty posture may operate disadvantageously even in bed (see SERVICE VOLUME, 1944) and, when present, needs attention and gentle measures of correction.

Replacement therapy often achieves striking, beneficial results in several hormonal fields. Unfortunately, the achievement of replacement therapy is by no means as simple as it sounds. Deficits may be suspected or known, but specific replacements may not be available for use. The whole chain of endocrine activities may be involved, from the pituitary to the adrenals and gonads, and it may be impossible to evaluate the predominantly active or depressive factors chiefly concerned. It is here that a critical use of rest in a strictly conditioned sense has been shown to have signal value. Indeed, from the clinical standpoint, the statement can be made that at present the only successful conservative approach to such multiple imbalance must be sought in the use of rest, with or without certain accessory factors which often condition or enhance its usefulness.

It is important to point out that physiologic rest may not be possible of inauguration or final achievement without pharmacologic assistance. The excited psyche and conditioned reflexes of the state under discussion will not return to normal quickly. Elevated nervous activities are usually in part defense mechanisms and are more easily aroused than allayed.

In this connection it may be well to mention that the use of "tonic" medication often has significant value in conjunction with gentle sedation in instituting a program of conditioned rest. Many clinicians feel that the administration of *strychnine* or *nux vomica* coincidentally with the *sedatives* is antagonistic pharmacologic practice. This is not the case, however, provided the dose of each is small.

There are some accessory habits and activities, accepted as part of normal living, which prevent or postpone operation of the favorable influences discussed. One of these is the use of tea or coffee, which are often allowed almost *ad lib*. It is important to realize that from the physiologic standpoint, drugs such as caffeine, nicotine, theine, and even theobromine make drafts or excessive demands on many kinds of tissue, especially perhaps the nervous. Such drafts may be as significant as excessive physical activity and may completely prevent the normal, not to say the restorative, influence of rest.

One needs only to be reminded that small doses of nicotine operate like acetylcholine to stimulate all autonomic ganglions. Large doses paralyze these ganglions and prevent passage of any impulses through them. The well-recognized influence of tobacco toward vasoconstriction serves to aggravate the pathologic vasoconstriction which is present in many cases of arthritis. The author's case histories contain ample proof that patients recognize this themselves, and some could hardly be induced to resume smoking after having stopped it for a few months. Mere reduction of smoking does not seem to have the same influence.

### Rehabilitation

According to Lyons and Coulter,<sup>15</sup> every large hospital should make some

provision for the rehabilitation of manpower which has been so vitally affected as the result of total war. It is not sufficient for the practitioner or surgeon to guide his patient through the acute stages of his malady or injury; his convalescence must also be planned and, through

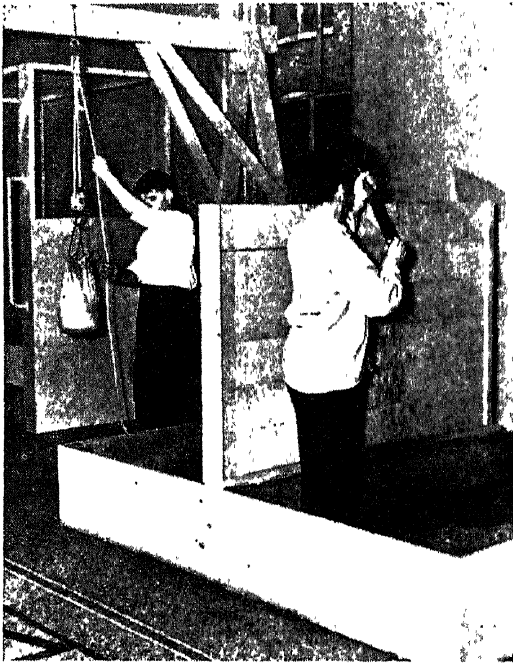


Fig. 3—A scaffold with adjustable pulley and a partitioned gravel pit which was constructed by hospital carpenter. (Coulter, J. S. and Lyons, L. M.: *The Modern Hospital* 65: 62 (Oct.) 1945.)

skilful guidance, be shortened in every way possible.

As we look ahead, many of our former industrial workers will return as veterans of this war and if they are injured they will need treatment in civilian hospitals comparable to that which was given them in the Army and Navy hospitals and which will continue to be given by the Veterans' Administration.

Insurance companies are beginning to recognize the need for this service and the Liberty Mutual Insurance Company, now writing a substantial volume of workmen's compensation, recently estab-

lished its own rehabilitation center in Boston.

St. Luke's Hospital, Chicago, established a rehabilitation center. Here the occupational therapy department was enlarged and kept in close proximity to the physical therapy department, a necessary and desirable relationship. This was accomplished by using an area which had in years past served first as a surgical ward and later as an employees' dining room.

This room was large, well lighted, and ventilated, with a high ceiling, and was easily connected with the physical therapy department by the construction of a steel stairway. This stairway was broken into units—five steps, a rest landing, and then six more steps, and was equipped with hand rails. This stairway in itself is a valuable asset in treatments.

This department has three rooms: A workshop,  $28\frac{1}{2}$  by  $62\frac{1}{2}$  feet, a recreation room, 23 by 42 feet, and a small storeroom. The workshop is equipped with a bicycle lathe and two bicycle saws, one treadle saw, and one treadle sander (built by the occupational therapy department from parts of old sewing machines), a scaffold with adjustable pulley for weight lifting, and a partitioned gravel pit which was constructed by the hospital carpenter. (Fig. 3.)

In addition there are three standard workbenches, a tool cabinet, a paint table, and two hand and two foot looms.

In addition to instruction in exercise through work therapy, the patient is taught to meet the physical demands of daily life. These demands, usually taken for granted by the average person, often loom so large to the disabled that his inability to cope with existing conditions constitutes a serious threat to his independent action.

Many times when patients are discharged from a hospital, they are walk-

ing 'on crutches without much preliminary experience. At St. Luke's, this instruction is started early by giving psychological and physical preparation in the use of crutches while the patient is still sitting on the bed. At that time



Fig. 4—Automatic street signal to teach patient to cross street on crutches. (Coulter, J. S. and Lyons, L. M.: *The Modern Hospital* 65: 62 (Oct.) 1945.)

crutches are fitted and the beginning of crutch walking on the level floor is started.

Crossing a street on crutches, with the traffic stopped but likely to start with traffic lights, presents to the patient a definite psychological and physical hazard. To meet this problem, the patient is taught to step down from a 9-inch curb and to walk 60 feet, which is the width of Michigan Avenue, timing his action with a standard automatic street signal that has been installed in the department. This signal was made available by the Chicago Safety Commission

and is extremely valuable. (Fig. 4.) When the patient reaches the far end of the room, or the width of the street, he steps up onto the curb.

To train a patient with crutches to get on and off the street cars, there was obtained, through the courtesy of the Chicago Rapid Transit Company, a standard street car step, handles and all, which had been mounted on a platform of standard height so that the patient learns by practice to get on and off transportation equipment. (Fig. 5.)

The authors believe that an adequate hospital rehabilitation center depends



Fig. 5—Street-car step to teach patient to board a street car. (Coulter, J. S. and Lyons, L. M.: *The Modern Hospital* 65: 62 (Oct.) 1945.)

upon proper personnel, proper equipment, good location, and complete coordination between the occupational and physical therapy departments of the hospital. Standards of care and treatment should be safeguarded by the employ-

ment of highly competent workers and by the appointment of a physician as director of the department.

The department should be staffed by registered physical therapists and registered occupational therapists.

To guard against fatigue, the patient is cautioned that exercise, whether work or play, should consist at first of rela-

through recreational activities. In addition, there are floor checkers for back exercise, for inversion and eversion of the ankle (Fig. 6); a wall checkers game and a darts game, for shoulder, arm, and hand action; table hockey for supination, pronation, and general coordination, and many other table games for intrinsic movements of the hand.

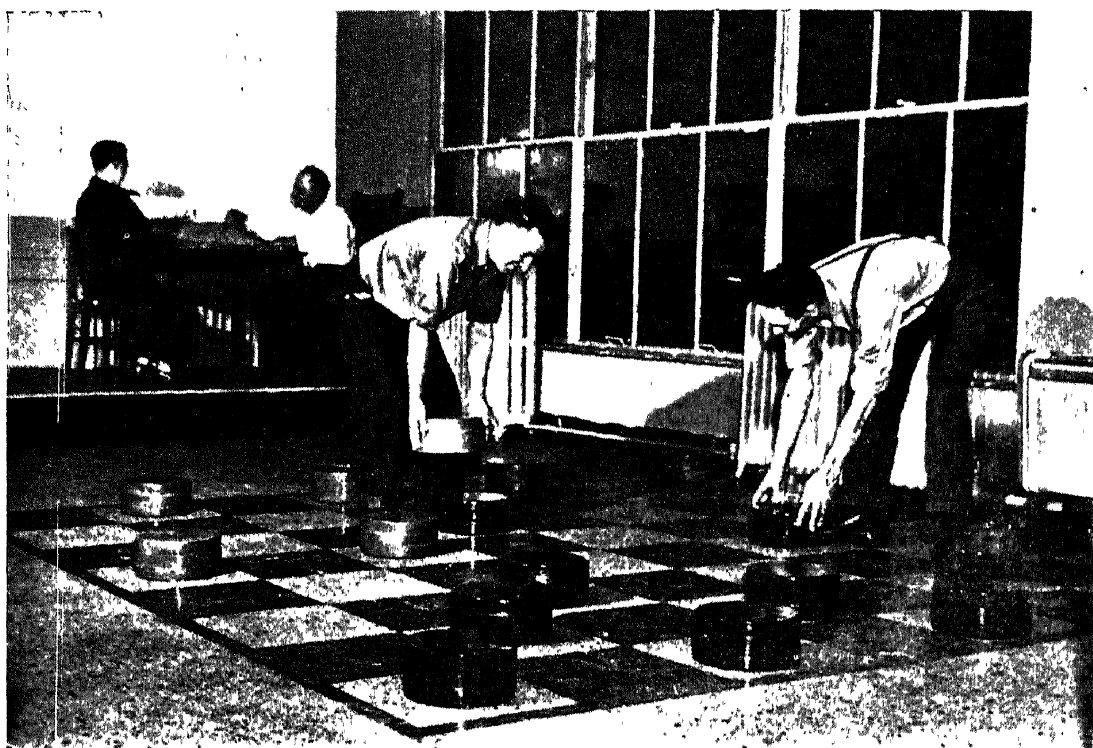


Fig. 6—Part of recreation room showing floor checkers. (Coulter, J. S. and Lyons, L. M.: *The Modern Hospital* 65: 62 (Oct.) 1945.)

tively short periods. It is recognized that fatigue may be mental as well as physical; therefore, recreational therapy is an important adjunct to this program. Recreational therapy, which is a form of occupational therapy, can be arranged to give desired exercise through the placing of special equipment.

In this department we have a pool table and a ping-pong table; these provide walking exercise, exercise of the hand and arm and general coordination

Besides these, there is an indoor and outdoor shuffleboard court, as well as a horseshoe pit, which are used for shoulder, arm, and general body exercise.

Another function of the recreation room is its contribution to the much-needed social adjustment of the patient.

**The Industrial Casualty**—The all-important factor in the treatment of any traumatic lesion is the element of time, according to Aitken.<sup>16</sup> It must be remembered that nature heals all injuries,

regardless of the tissue involved, by scar tissue. Consequently, when an injury has involved skin, fat, muscles, tendons, nerves, and bones, as in compound fractures, all the structures become healed in a mass of scar tissue. Adhesions thus are formed between all these structures and interfere with their free play. With time, scar tissue contracts and becomes more and more dense and less and less elastic. Consequently, unless such adhesions are broken or stretched by early motion, they may become so dense and tight that normal function may never be regained. The importance of early motion can thus be seen.

When any part is immobilized in apparatus, two other important changes occur. First, there is a gradual loss of joint motion.

The second condition is the development of muscle atrophy.

When a patient with an acute condition is admitted to the center, he is first sent to the physical therapy department. Here *baking*, *massage*, and graduated *exercises* are given until sufficient strength and motion have returned to permit of some occupational therapy. Such treatments are carried on after the patient has started his work therapy if necessary. As the work tolerance is built up, the physical therapy is cut down, while the work therapy is increased. The physical therapy department is quite complete, and almost any form of physical therapy can be administered. Shoulder wheels, stall bars, resistance bicycles, pulleys and weights, and a rowing machine are available for special exercises.

On admission to the occupational therapy department, the patient is given actual work to do. The work is always done with the aim of increasing the strength and range of motion of the injured part.

### Resuscitation

Lapin<sup>17</sup> states that the adoption of the rocking method of resuscitation by the Royal Navy has aroused much interest. In view of the success of the Schaefer technic, used routinely in the United States, experiments were conducted and a method devised, it is believed, which incorporates the best points of both methods and represents an ideal technic of artificial respiration.

A folding trestle is attached to the sides of a standard Army litter. When opened and secured, the litter is supported on this "horse," fulcrumed as if it were an old-fashioned seesaw.

The subject is placed face downward on the litter, after loosening his constricting clothing, belts, collar, and necktie.

The advantages of this method are: Accessibility and ease of operation with no fatigue to the operator; pressure equal, easily regulated, and maintained; massage with tonic effect on the cardiac musculature; compression of the thoracic cage at the exact time that the diaphragm is being pushed upward by the weight of the intestines; quick release of pressure on the thorax while the diaphragm is dropping, allowing for expansion of the lungs to their fullest extent; increased circulation to the brain with therapeutic effect on concurrent cerebral anemia (shock); easily improvised; ability to keep patient warm and dry by covering during resuscitation; easy transportation of apparatus.

### Burns

Where applicable on limbs, Siegel<sup>18</sup> has made use of the *whirlpool bath* to aid in separating sloughs and to improve vascularity under healed areas, which have been skin grafted, as soon as they will tolerate moisture.

Contractures are combated by placing the limbs in extension and splinting them

to prevent muscle spasm inducing contractures. If the dressings are voluminous enough, they will sometimes be sufficient, provided they are made comfortable, which the thick grease dressing does. Where feasible, *elevation* is arranged by suspension from an overhead fracture frame, which permits movements, active and resistive, at the earliest possible time. These "resisted" *exercises* are used in flotation to overcome muscle spasm and increase the range of motion of major joints. With the aid of pulleys at each end of the bed and light, graduated traction weights, the extensors and flexors are exercised alternately and independently. The value of this type of muscle exercise has been little appreciated. Siegel has used them successfully in many types of injuries.

Such exercise tends to diminish all the factors which predispose to spasm, atrophy of tissue, and contractures, thus avoiding some of the sequelae of burns. The cooperation of the patient in doing these exercises cannot be obtained unless these movements are without pain or discomfort.

### Gonococcal Arthritis

Twenty-three cases of drug-resistant gonococcal arthritis are reported by Solomon.<sup>19</sup> Of these, ten patients were treated with *sulfonamides* and *artificial fever* in the *hypertherm* with the following results: Four were cured and the remainder showed either considerable or partial improvement. Fifteen were treated with sulfonamides and artificially induced fever with *intravenous typhoid vaccine* with the following results: Six were cured, six were either considerably or partially improved; three were not benefited; two of the latter were subsequently treated in the hypertherm with good results.

The result with both of these methods was encouraging. The use of the hypertherm is preferable to the use of vaccine. The most important consideration, however, is early treatment. Hence, if the hypertherm is not available, combined vaccine and sulfonamide therapy should be instituted without delay.

It is emphasized that specific therapy does not supplant the regular methods of management of arthritis which include *bed rest*, special *diet*, and *physiotherapy*. Specific therapy is used in addition to these and results in a much greater percentage of cures and in the restoration of joints to useful function.

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## RESPIRATORY DISEASES

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### Histoplasmosis

The literature on respiratory diseases during the past year evinces greater interest than has been shown previously in the fungous infections of the lungs. This is particularly true of histoplasmosis, which, while it is a systemic infection with protean manifestations, frequently produces symptoms, due to invasion of the lungs by the causative agent, *histoplasma capsulatum*.

**Pulmonary Calcifications** — The present interest in human infection with *histoplasma capsulatum* resulted from mass surveys by roentgen examinations of the chest of enormous numbers of individuals being examined for induction into the armed services. The presence of calcifications, observed in roentgen studies of the chest, resulted in the rejection of many individuals otherwise qualified for active service.

In the past, such pulmonary calcifications were considered to be caused solely by pulmonary tuberculosis, and although their presence was regarded as being indicative of healed lesions, candidates were arbitrarily rejected on the basis of the size or number of these roentgen shadows. It was natural to assume that individuals with large or multiple calcifications, all of which were thought to be due to previous tuberculous infection, would under the stress of military service show a greater tendency than those without calcifications, or with minimal ones, to develop active disease.

Much doubt of the correctness of this deep-rooted opinion, shared by internists, phthisiologists, and roentgenologists, that all pulmonary calcifications were caused by healed tuberculosis, was expressed by Long and Stearns (1943),

who, basing their opinion on Selective Service records, found that the incidence of calcifications, as observed by roentgen studies of the chest, showed geographic variation, completely uncorrelated with the prevalence of known tuberculous infection. Furthermore, they found that a large proportion of persons with these lesions had negative tuberculin reactions. These observations quite naturally led to a search for other causes of pulmonary calcifications. In 1943, Smith observed that the geographic area of high prevalence of pulmonary calcifications in tuberculin-negative persons corresponded with an endemic area of histoplasmosis.

A very significant contribution by Palmer<sup>1</sup> has appeared on this subject during the past year. It is based on an extensive investigation of tuberculosis in student nurses conducted cooperatively by the National Tuberculosis Association, the United States Public Health Service, and a large number of tuberculosis specialists. Approximately 10,000 student nurses in 65 schools, in 9 widely scattered metropolitan centers, were examined by chest films and tuberculin tests. These studies showed clearly the marked geographic regional differences in the incidence of pulmonary calcifications, and also that in certain states the majority of those with calcifications did not react positively to tuberculin.

In an attempt to determine the etiology of the calcifications found in this group, it was decided to study their reactions to various fungi. Intracutaneous tests with coccidioidin (1:100) were given to a small number, with essentially negative results. Following this, a group of 3105 student nurses was

organ, such as the adrenal. The skin, the anal canal, the middle ear, the pharynx, the larynx, the lungs, the intestinal tract, the liver, the spleen, the bone marrow, and even the endocardium, have shown lesions during life and at necropsy, resulting from the invasion of this fungus. "Irregular, low or moderate fever was present in forty-seven of forty-nine cases; hypochromic anemia in forty-four of forty-six; palpable liver in thirty-nine of fifty-one cases; palpable spleen in thirty-seven of fifty-one cases; enlarged lymph nodes in twenty-nine of the forty-two cases in which they were mentioned; leukopenia in twenty-eight of forty-eight cases." "Lesions of the lungs have been noted in thirty-four of the sixty-one cases analyzed—ulcerative lesions of the oropharynx were present in twenty-one of the sixty-one; ulcerations of the skin in nine."

"In each of the seven cases in which the values of blood proteins have been recorded, they have been abnormal: Low total protein in three cases and reversal of the albumin-globulin ratio in four." This may be a useful diagnostic test, although certain other diseases, Boeck's sarcoid, multiple myeloma, leukemia, and sometimes cirrhosis of the liver, all of which may have certain clinical features in common with histoplasmosis, may show reversal of the albumin-globulin ratio.

From what has been found both during life and at necropsy, it is obvious that histoplasmosis is capable of imitating many more common diseases, such as tuberculosis, aleukemic leukemia, Hodgkin's disease, and malignant neoplasm. In three cases, vegetative endocarditis has resulted from invasion of the heart valves by *histoplasma capsulatum*.

According to Parsons and Zarafonetis, successful diagnosis during life has most

often been achieved by histologic study of biopsy material and culture of the organism from it. In five instances, the organism has been obtained from the sternal bone marrow. Occasionally, and late in the disease, *histoplasma capsulatum* has been found in blood smears and by blood culture. It has been recovered from the sputum in one instance.

In most cases, the duration of symptoms averages five months. Occasionally, where the disease has been limited to chronic ulcerative lesions of the skin, the infection has lasted as long as sixteen years, before terminating fatally. Four of the patients recorded by Parsons and Zarafonetis are still living after intervals of two to six years, but in three of these, ulceration of the tongue was the only known site of infection. These authors are of the opinion that histoplasmosis is a unique fungous infection in that the yeastlike form attacks or is attacked by the cells of the reticuloendothelial system. Because these cells are present almost universally in the body, one must expect to find parasitized macrophages in almost any tissue.

It is believed that although the treatment of this disease is still in the experimental stage, certain antimony compounds and a new diamidine preparation may prove at some future time to be effective.

The author of this review on the diseases of the respiratory tract desires to emphasize the probable correctness of the opinion that many, and perhaps most, pulmonary calcifications, especially in certain geographic areas, are not tuberculous in origin. They may be produced either by previous infection with *histoplasma capsulatum* or by some other as yet unrecognized immunologically related organism.

It is hard to believe that all persons reacting to *histoplasma capsulatum*, of



which there must be more than a million in the United States, exhibit this skin sensitivity as the result of subclinical infection with this fungus, when there are so few clinical cases of histoplasmosis (less than 100) recorded in the world's literature. Furthermore, those exhibiting sensitivity to this infective agent are apparently in normal health, whereas those afflicted with the disease in its fully developed form almost without exception succumb rapidly to it. But perhaps infection with histoplasma capsulatum is analogous to that produced by the tubercle bacillus, in that in the latter the disease may be manifested by calcified healed lesions or localized infection of lymph nodes, or by fulminating hematogenous miliary spread with meningeal involvement and rapid death.

### **Treatment of Chronic Respiratory Diseases**

#### **Use of Penicillin Parenterally —**

The established value of penicillin administered parenterally in the treatment of acute respiratory infections due to various gram-positive organisms has, quite naturally, resulted in the therapeutic trial of this drug, similarly administered, for the prevention and treatment of various chronic diseases of the respiratory tract.

White and his associates<sup>5</sup> have reported a carefully controlled study of the use of penicillin in the prevention of postoperative empyema. Prior to partial single or multiple lobectomy or pneumonectomy, twenty-one patients received 150,000 units of penicillin daily by intramuscular injections at two-hour intervals for one week preoperatively and for two weeks postoperatively. Twenty patients similarly operated and not given penicillin served as controls. Pyogenic empyema did not develop in any of the twenty-one patients treated with peni-

cillin, while twelve (60 per cent) of the controls developed pulmonary suppuration with empyema. In the entire group, there were twenty-one who had partial or total lung resection for bronchiectasis or multiple lung abscesses. None of the twelve treated with penicillin had intrapleural infection. All of the nine in the control group developed empyema. In three of these it is stated that the infection was overwhelming and contributed to the death of these patients.

None of the treated patients developed bronchial fistulas; three occurred in the control group. There were no wound infections in the treated cases, compared to four such instances in the controls.

There were fifteen patients who had partial or total lung resection for tuberculosis; seven treated and eight controls. Tuberculous empyema developed in two of the treated patients, and in three of the controls. There were five patients operated for bronchogenic carcinoma, two treated and three controls. None of them developed empyema.

In view of these results, the authors conclude that penicillin prophylaxis has its greatest usefulness in those cases in which there is pyogenic pulmonary suppuration.

Kay and Meade<sup>6</sup> have reported their results in a series of ninety-three patients with chronic infections of the lungs and bronchi treated with penicillin. Included in this group are forty-five patients with bronchiectasis, seventeen with lung abscess, six with suppurative pneumonitis, nineteen diagnosed chronic bronchitis, and five with fungous infections. Patients with bronchiectasis and chronic bronchitis were treated at first by intramuscular and later by intratracheal penicillin. Excellent results were achieved in those considered to have chronic bronchitis; this diagnosis being based on bronchoscopic visualization and normal

other routes of administration, they emphasize the fact that the inner surface of the lung has an area 500 times as great as the body surface, and absorbs so rapidly as to give an effect similar to that which results from intravenous injections. By using India ink or radioactive substances as indicators, it has been found that the aerosol penetrates to the outermost pulmonary alveolae.

They treated six patients with severe infective bronchial asthma. They found that the penicillin-susceptible organisms disappeared promptly from the sputum, but that the disease was not influenced materially. Prompt symptomatic improvement was obtained in the treatment of five patients with bronchiectasis. They are of the opinion that in the palliative treatment of this disease, penicillin aerosol is more effective than when it is administered parenterally.

Segal and Ryder advocate the long-continued use of penicillin aerosol in all cases of acute solitary abscess or multiple lung abscesses, and believe it should be tried in chronic lung abscess, although it is not likely in these cases to be of curative value.

### **Treatment of Bronchial Asthma**

**Use of Penicillin**—During the past year, a number of contributions have appeared on the therapeutic use of penicillin in chronic infective bronchial asthma. Very properly, penicillin therapy has been limited almost without exception to the intrinsic type of bronchial asthma, believed by many to be an expression of true bacterial allergy. Reference has already been made to the observations recorded by Barach and his associates,<sup>8</sup> and those of Segal and Ryder,<sup>11</sup> who treated, respectively, five and six cases of chronic infective bronchial asthma by penicillin aerosol.

One of the first contributions on the treatment of chronic allergic disease with intramuscular penicillin is that of Schonwald and Deppe.<sup>12</sup> Their uncritical selection of eighty-six allergic patients for treatment, their technic of administration of penicillin, "when commercial penicillin was obtained, this was used in thirteen cases, 2500 units given intramuscularly two or three times a week," and the unwarranted optimism expressed by these authors after a too brief follow-up period, make further review of this publication unprofitable.

Hampton and his associates<sup>13</sup> treated nine patients with chronic intrinsic bronchial asthma with intramuscular penicillin. All of them were moderately or severely asthmatic. They were observed for four weeks prior to therapy, during treatment, and for four weeks thereafter. Each of five patients received a total of only 500,000 units intramuscularly. In addition, all of the nine patients received intratracheal penicillin. Hampton observed slight clinical improvement in four of his cases. However, in his opinion, penicillin, administered intramuscularly or intratracheally in the doses used by him, was of little or no value, and offers no advantage over other types of therapy in the treatment of intrinsic bronchial asthma.

Leopold and Cooke<sup>14</sup> have published a preliminary report on the treatment of intractable bronchial asthma with penicillin. They cite two case reports of patients with severe chronic intrinsic asthma who experienced marked temporary relief following the administration of full doses of penicillin by intramuscular injection.

One of these patients (Lc), who for fifteen years required one or more injections of epinephrine daily, was so much improved that no epinephrine was used for seven months after penicillin

therapy. (This patient has since relapsed and a second course of penicillin, orally administered, has been without effect.) These authors have used penicillin intramuscularly, minimum total dose 1,000,000 units, in twenty-five additional cases of intractable intrinsic bronchial asthma, with no relief in some, marked temporary improvement in others, and "cure" in none.

From a critical review of the current literature of the past year on the therapeutic effects of penicillin, administered intramuscularly or by aerosolization, in various chronic diseases of the respiratory tract, it is permissible to draw certain tentative conclusions.

It probably makes little difference, assuming adequate dosage, and proper technic, whether penicillin is administered parenterally or by aerosolization in the preoperative preparation and during the postoperative period in patients subjected to pulmonary resection for suppurative or malignant disease of the lungs. None of these patients treated intramuscularly by White<sup>4</sup> and his associates developed empyema, and only one patient in Olsen's<sup>10</sup> series treated by aerosolization developed this complication.

It is probable that penicillin is totally ineffectual in preventing spread of tuberculous infection in those thought suitable for pulmonary resection for this disease. This was White's experience in this group of cases, and although there are no other recorded instances of the use of penicillin aerosol under similar circumstances, it was predictable that this method would be futile, as penicillin is not bacteriostatic against the tubercle bacillus.

Penicillin by aerosolization may be more effective than by intramuscular administration in the preoperative preparation of patients with chronic lung ab-

scesses, because, by nebulization high concentrations of penicillin can be introduced directly into the diseased areas, providing that the bronchi draining them are patulous. As Barach has stated, this form of treatment may be analogous to the local instillation of penicillin into the pleural cavity for the nonoperative treatment of empyema. It is quite possible that an occasional case of solitary abscess or of multiple abscesses may respond favorably to penicillin aerosol and not require surgical intervention.

There appears to be no choice between parenteral and aerosolized penicillin for the treatment of advanced bronchiectasis. Both are palliative, but when the disease is too widespread for pulmonary resection, penicillin by either route is a valuable method of symptomatic therapy. As Olsen has stated, streptomycin by either route of administration may prove to have a comparably beneficial effect in temporarily eradicating gram-negative organisms in chronic pulmonary infections.

Recently, a patient with chronic Friedländer infection of the lungs has been treated with streptomycin aerosol, with prompt disappearance of these organisms from the sputum. Insufficient time has elapsed to permit deductions to be drawn in regard to the length of time that this will continue to be true.

In the treatment of chronic infective bronchial asthma, the use of penicillin by intramuscular injection, or by aerosolization, has been followed in a good many cases by a variable period of definite or even dramatic clinical improvement. Almost all of these patients have relapsed and have not benefited from a second course of penicillin. It is probable that relief in these cases was achieved by temporarily ridding the respiratory tract of penicillin-sensitive organisms, only to have the patient relapse when

indicated for those who have had non-fatal pulmonary embolism, even in the absence of positive signs of venous thrombosis in the legs. Operation is, of course, advised for those with positive signs of phlebothrombosis. Prophylactic femoral vein interruption has been advised under certain circumstances. The operation should be bilateral. Finally, the morbidity of thromboembolic disease has been reduced tremendously by femoral vein interruption, and there have been no deaths in the 464 patients who have been operated.

### **Ligation of Inferior Vena Cava for Prevention of Pulmonary Embolism**

Allen and his associates<sup>15</sup> reported 579 interruptions of the femoral veins; the superficial femoral in 480 instances, the common femoral in 99. These veins are easily accessible, and in early cases they can usually be interrupted above the level of the thrombus.

When the thrombus extends higher, Homans<sup>16</sup> prefers to ligate the common iliac vein through an extraperitoneal approach, although this is adaptable only for unilateral operation. In the presence of bilateral thrombosis of the common iliacs, Homans suggests ligation of the inferior vena cava. Another indication for this operation, according to Homans, is the prevention of pulmonary embolism in those relatively infrequent instances where its source is the pelvic veins. In 1943, Collins *et al.* reported eight cases of ligation of the inferior vena cava for pelvic thrombophlebitis, with one death. Within the past year, Gaston and Folsom<sup>17</sup> performed this operation successfully in two patients who had had multiple pulmonary infarcts as the result of femoral thrombosis.

The first patient was a woman forty-nine years of age who was admitted to the hospital with extensive burns of both thighs. She was confined to bed for twenty-two days. On the twenty-seventh day, she developed pulmonary embolism, as the result of which both common femoral veins were ligated. Despite this, she had another major episode of pulmonary infarction. The inferior vena cava was ligated under spinal anesthesia. The patient recovered after a stormy convalescence, and four months later there was no longer distention of the collateral veins and edema of the lower extremities.

The second patient was a man, seventy-one years of age, with thrombophlebitis of the left leg, secondary to a draining sinus and a cellulitis of the foot. Three days after surgical drainage of the cellulitis, he developed pulmonary embolism, manifested by intense pain in the lower abdomen. Middleton (1943) has described this same location of pain in a few cases of pulmonary embolism. Subsequently, the diagnosis of femoral thrombosis was reasonably established by the appearance of induration in the left calf and thigh. The common femoral vein was explored and found tightly thrombosed. When the clot was removed, it was found that the intima of the vein was injured and would, therefore, have been the probable source of further thrombosis and embolism. Consequently, the inferior vena cava was ligated. Three months later the patient was well except for slight residual edema of the left leg. Gaston and Folsom are of the opinion that "ligation of the inferior vena cava below the level of the renal veins is a safe procedure and is effective in preventing embolic sequelae of thrombosis of pelvic veins, whether primary or secondary to a propagating thrombophlebitis originat-

ing in the leg veins. Adequate collateral circulation develops and edema eventually disappears."

The author of this review on the current literature of diseases of the respiratory tract desires to emphasize the importance of recognizing the diagnostic features of pulmonary infarction in its sublethal manifestations. He also believes that one must maintain a high level of clinical suspicion, and remember to carefully and frequently examine the lower extremities, especially postoperatively, for evidences of bland thrombosis. It is only in this way that the tragic postoperative deaths from massive occlusion of the pulmonary artery can be prevented.

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## TROPICAL MEDICINE

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This review aims to bring to attention a few of the more noteworthy and promising advances in tropical medicine during the year 1945. Advance has been rapid and reports numerous in this field, particularly with reference to those diseases acquired in considerable numbers by members of the armed forces in tropical and subtropical theaters of war. Because of this new interest and responsibility, we find most medical journals here and abroad well nigh flooded with publications on these subjects. Hence completeness of review is out of the question. In preparation of this paper, review journals have been freely used, in particular the excellent *Tropical Diseases Bulletin*.

The war has furnished unparalleled opportunities for the study of certain diseases. Where large bodies of troops have acquired infections to which they had never before been exposed, results have often been striking and unexpected. There have appeared new disease characteristics, unknown or unrecorded for these same diseases as observed in the usual chronically infected inhabitant of the tropics. Then, too, completely equipped medical units have been so placed as to bring to bear in investigation the most modern thought and methods, while at home and abroad research has been concentrated on these most urgent disease problems. Among the disease entities exhibiting surprise features we may list in

particular malaria, filariasis, schistosomiasis, hookworm infection, and the rickettsial diseases, especially scrub typhus.

### Malaria

Though malaria is well known in our own southern states, the experience of having whole armies laid low with malarial attacks and relapses was new and unexpected. Out of bitter experience we have learned much that is new. We have come to an appreciation of differences in malaria strains and are now aware that South Pacific strains of *vivax malaria* are relapsing strains above all others in our previous experience. Through the months since their infection, many of our troops have continued to have their relapses, up to twenty-five or thirty in number, over periods of one, two, or occasionally three years. It is calculated that with these South Pacific strains a patient has in each attack about a 70 per cent chance of having another. With Mediterranean malaria, on the other hand, the chances are only about 30 per cent. With malaria posing for us questions of this magnitude, answers had to be found and such answers have appeared with amazing rapidity. Laboratory and clinical investigation in many centers and outlying posts have brought their contributions in the face of a desperate need when we found ourselves losing a war, at least in certain areas, as the price of failure to control one disease.

It is difficult to realize from the vantage point of a year's progress, the uncertain state of our knowledge a little over a year ago with regard to the use of *atabrine*, its dosage requirement for suppressive therapy, its dependability for that purpose, its superiority over quinine for suppression and for treatment, and its low degree of toxicity. At present, all these facts are firmly established. The

suppression dosage schedule of 0.1 gm. daily is generally accepted. Break-through of malaria attack on such a schedule is looked upon as failure of atabrine discipline, not of atabrine.

Only a few of the outstanding contributions to this subject can be described even briefly. Brilliant in scope of planning and in execution is the work of Fairley<sup>1</sup> in tropical Queensland. To determine the precise value of *quinine*, *atabrine*, and certain *sulfonamides* (diazine, merazine, and methazine) as suppressants and as true causal prophylactics, volunteers taking the drugs in various dosages were exposed to bites of malaria-infected mosquitoes and the effect observed. Volunteers were restricted to men who had never lived in malarious regions. Mosquito vectors were mainly *Anopheles punctulatus*, var. *typicus*, larvae of which were collected in New Guinea and flown to Queensland. Among the large number of volunteers used, none were found to possess natural immunity, demonstrating, it is believed, that at least for Europeans not previously exposed to the disease, there is no such thing as refractoriness to infection if viable sporozoites or trophozoites are injected in sufficient dosage.

*Atabrine*, 0.1 gm. daily, was compared with *quinine sulfate*, 0.6 gm., and with *sulfonamides*, 1.0 gm. Only atabrine certainly suppressed either *falciparum* or *vivax malaria* and certainly cured *falciparum* when continued twenty-three days after the last exposure. None of the drugs was able to cure *vivax malaria* and attacks appeared within a few weeks of discontinuance.

Some of the facts are made comprehensible by the assumption, not yet proved, that human malaria is similar to *avian malaria* in having a tissue phase. It would then seem that parasites in the tissues are protected from attack by

antimalarials, also that the tissue phase of falciparum is short; of vivax, very persistent. In his experimental work, Fairley frequently used subinoculations of 200 cc. or more of blood to determine its infectivity. Seven minutes after volunteers were bitten on one arm by infected mosquitoes, blood was taken from the other arm and produced malaria. This occurred with either falciparum or vivax infections. Thirty minutes after the bite, the blood was noninfective and remained so until the seventh day with falciparum, the ninth with vivax. Obviously, the seven-minute infections were due to circulating sporozoites and the later ones to trophozoites, the parasites presumably being hidden away in the tissues in the interval.

Plasma atabrine levels were measured in thirty-five volunteers taking 0.1 gm. a day for 168 days. Gradual build-up was observed up to the fourth to sixth week, then maintenance at that level, with a mean concentration of 21.9  $\gamma$  per liter (range 7 to 90  $\gamma$ ). No break-through of malaria occurred. After discontinuance there was a gradual fall, about 10 per cent a week, reaching zero in about six weeks.

The knowledge obtained by Fairley's experiments was at once put to practical use, with the result that the December, 1943, malaria rate of 740 per 1000 per year in Australian troops in New Guinea dropped to 26 per 1000 per year by November, 1944. Other causes contributed to the drop, but absence of frequent vivax relapses was evidence of the important rôle of *atabrine*.

In discussion of this paper, Findlay reported an almost complete absence of black water fever in Europeans in West Africa since atabrine, and atabrine alone, has been used in suppression and in treatment. He has noted only two cases in Europeans in the last year, one in

an officer who took *quinine* instead of *atabrine* for suppression and for treatment in each of four malaria attacks.

Another intensive piece of work on a large scale has been done under direction of Duncan,<sup>2</sup> who found malaria attack rates of over 3000 per 1000 per year not unusual in combat units in New Guinea even though suppressive treatment with *atabrine* was being prescribed. A training center established in Australia to rehabilitate soldiers with recurring malaria for further combat provided opportunity under absolute control for determining the efficacy of atabrine at various dosage levels. Sixteen groups of 151 to 267 persons each were used in the study. Drug effectiveness and plasma levels were found to be unaltered by heavy physical exertion. Complete suppression of malaria attacks was attained when patients received 0.1 gm. *atabrine* daily or 0.4 gm. twice a week. A single 0.5 gm. dose weekly was unsatisfactory. Untoward reactions were unimportant. Yellow staining of skin appeared in about 20 per cent of patients after several weeks and disappeared gradually in six to ten weeks when the drug was discontinued. Staining of the sclerae was noted in about 1 per cent of cases and differed from jaundice in showing the deepest color in exposed portions of the sclerae. Gastrointestinal difficulties were minimal and transient when the drug was taken after meals unless there had been preexisting mental disturbances or chronic gastrointestinal disorders.

This controlled study proved beyond doubt that failure of *atabrine* suppression at the front resulted from failure of discipline. Thereupon selection was made of a battalion in the field having a malaria record which ran 130 to 1230 attacks per 1000 per year from August to November, 1943, in spite of the dis-

tribution of *atabrine*, 0.1 gm. daily, six days a week. In December, 1943, each man in the battalion received 0.5 gm. twice a week under direct supervision. The attack rate dropped to zero within twenty-four hours and stayed there during the following months. Enforcement of the original 0.1 gm. daily dose would have accomplished the same results though a little more slowly and less dramatically. The author concluded that a platoon officer could rid his platoon of attacks of malaria by spending fifteen minutes twice a week in seeing that every man received his medicine. As with the platoon, so with an army.

Shannon and Earle<sup>3</sup> draw attention to the fact that when *quinine* is used for suppressive therapy it takes 1.0 gm. daily to give results equivalent to those obtained with 0.1 gm. of *atabrine*. Plasma levels of 5.0 mg. per liter of quinine are needed as compared with about 30  $\gamma$  of *atabrine*. In acute attacks of malaria, vivax trophozoites are completely cleared from the blood when *atabrine* plasma levels of 30  $\gamma$  per liter are maintained for four days or more. Falciparum is more resistant and requires approximately 50  $\gamma$  per liter for at least six days. If *plasmoquine* is to be used, the most serious of the toxic reactions, hemolysis, can be avoided by prescribing the drug for three days instead of five, 0.01 gm. t.i.d., without, it is claimed, loss of effectiveness in destroying falciparum gametocytes. The Reviewer believes that, as *atabrine* is now known to cure falciparum completely, the use of *plasmoquine* is usually unnecessary. An exception is mentioned below.

As a result of the investigations described and others, accepted standards for the use of *atabrine* are now as follows. For suppression, 0.1 gm. daily is given throughout the period of exposure and for an additional four weeks

after the last exposure. This dosage provides complete suppression of acute attacks of malaria at the time and will completely cure falciparum infections. Vivax infections, on the contrary, are suppressed but not cured.

**Treatment**—For treatment of an attack of malaria, initial or relapsing, *atabrine* is given in dosage of 1.0 gm. the first day in divided doses, an initial 0.4 gm., followed by 0.3 gm. at four-hour intervals for two doses. For the next three or four days, the dosage is 0.1 gm. t.i.d. This gives a total dose of 1.9 to 2.2 gm. Prolongation of treatment cannot prevent relapses of vivax infections, and such relapses, when they occur, are to be treated like the initial attack. If the malaria attack is due to *P. falciparum*, however, *atabrine* should be continued for four weeks in suppressive dosage, which treatment will effect a cure.

*Quinine* is inferior to *atabrine*. As a suppressive drug, it is much less certainly effective in tolerated dosage. Used for treatment of an attack, it gives shorter symptom-free intervals between relapses than does *atabrine*. Such intervals average about one month with quinine, about two months with *atabrine*.

By the use of loading doses of *atabrine* on the first day, early effectiveness of therapy is assured and the need for quinine almost eliminated except in the rare case of true sensitivity to *atabrine*. Quinine may nevertheless be needed for parenteral injection in those patients who are unconscious, delirious, or manic where oral therapy is not feasible and in those in whom vomiting or diarrhea would prevent absorption from the gastrointestinal tract. Under these circumstances, *quinine dihydrochloride*, 0.6 gm., is given by vein, slowly in 500 to 1000 cc. saline or 5 per cent glucose and repeated every six to eight hours as



needed. An alternative choice is *atabrine dihydrochloride*, 0.2 gm. in 10 cc. distilled water injected intramuscularly into each buttock. In these severely ill patients it may be wise to combine the two methods for the first dose. A number of patients have been treated by Machella<sup>4</sup> by using atabrine dihydrochloride intravenously, giving the drug in 1000 cc. 5 per cent glucose over a period of four hours. No untoward results were observed. In any case, oral therapy should always replace the parenteral route as soon as possible.

A new drug shortly expected on the market, *chloroquine*, *SN7618*, *arelen*, has certain advantages over *atabrine*. It does not stain the skin. It controls symptoms rather more rapidly and postpones relapses about ten days, on the average, beyond the period noted for atabrine. It suppresses and cures attacks in fewer doses than does atabrine. As a suppressant, 0.3 gm. once weekly is sufficient. For treatment of an attack, two doses of 0.3 gm. each are given the first day four hours apart, then 0.3 gm. daily for three days. This is adequate for any malaria attack and cures falciparum malaria completely. Toxic effects are minimal but may occur especially if the first day's dosage is pushed up beyond 0.8 gm. Occasionally there is mild nausea. Pruritis may appear, particularly the first or second day, often confined to palms and soles and in only a small percentage of patients associated with any visible skin lesions, as urticaria or dermatitis.<sup>5</sup>

The one outstanding failure in present-day antimalaria therapy is the failure of any known drug or combination of drugs to prevent the appearance and relapse of vivax malaria attacks once suppressive therapy has been discontinued. Put in other words, the doctor cannot cure vivax malaria. Relapse succeeds re-

lapse for months or years until the patient finally builds up sufficient immunity to eradicate the disease. At present, we are at a loss to meet this difficulty. We badly need drugs which in safe dosage will accomplish two things: first, prevent malaria infections by acting as causal prophylactics to destroy sporozoites injected by the mosquito, and second, prevent relapses of established vivax malaria, presumably by action on the reservoir of parasites in the tissues. Certain promising drugs for this purpose are now under investigation. Meanwhile, at any time when it becomes imperative to interrupt the relapse cycles, as in a patient requiring an operation, or one ill with another disease, *atabrine* may be used in suppressive dosage, starting some days before the anticipated need.

Reports recently released<sup>6</sup> indicate that *plasmoquine* exerts a unique effect in vivax malaria. In about sixty patients treated in an Army hospital during attacks of vivax malaria, it was found that *quinine* combined with *plasmoquine* in comparatively large doses and for a longer period of time than usual was effective in cutting down the relapse rate of vivax malaria from 80 per cent to less than 10 per cent. The drug was used at a dosage level of 0.02 gm. *plasmoquine naphthoate* along with 0.6 gm. *quinine sulfate* every eight hours for two weeks. This dosage is high and carries definite risks. Any patient in whom it is used should be in hospital. It should not be considered for routine treatment but used only in selected cases having proved relapses at very frequent intervals. Toxic effects to be looked for from *plasmoquine* include *abdominal cramps*, development of *methemoglobinemia* and *cyanosis*, *acute hemolytic anemia*, and *leukopenia*.

Fear of liver damage from the use of atabrine apparently arose because the yellow color produced in the skin suggested jaundice. This fear has proved groundless even in those taking suppressive therapy for a year or more. Persons who by accident or intent have ingested many times the therapeutic dose of the drug have usually recovered, and, if so, have as a rule shown no residual damage. Markson and Dawson<sup>7</sup> report the case of a European soldier, twenty-nine years of age, who in a fit of depression swallowed 25.0 gm. of atabrine. After ten minutes he vomited a number of times and developed diarrhea, then became weak and drowsy. He was seen three hours after taking the drug and found stuporous and in collapse. Yellow fluid was washed out of his stomach. Laboratory studies were not remarkable except for an 18,000 leukocyte count and a plasma atabrine of 906  $\gamma$  per liter. There was no atabrine in the cerebrospinal fluid. He was given 1000 cc. 30 per cent glucose in saline i.v. over four hours and had recovered by the following morning. Plasma atabrine on the third day was 183  $\gamma$  and on the fifth day 90  $\gamma$  per liter.

Atabrine in usual dosage is largely innocuous. It is recognized, however, that it may at times manifest toxicity in certain unusual forms. Under the title "Untoward Reactions Attributable to Atabrine," Livingood and Denaide<sup>8</sup> report conclusions to date. Skin lesions due to atabrine were first reported from the Southwest Pacific area in soldiers from New Guinea and nearby islands, and have since been seen in Assam and North Burma. In other malarious regions, where suppressive atabrine was being used, they were seen in but comparatively small numbers. The skin disease has been called "atypical lichen planus" and is characterized by vari-

ous combinations of these types of lesions: violaceous and erythematous hypertrophic lichenoid papules and plaques, frequently with a rough verrucous surface; violaceous and erythematous oozing or scaling eczematoid plaques; flat squamous geographic plaques on trunk, axillae, and groins similar to tinea lesions; white, sometimes violaceous tinged, slightly elevated mucous membrane lesions identical with those seen in typical lichen planus; oozing intertriginous dermatitis in groins and axillae and on posterior surfaces of the ears; ecthymatous lesions; scaling and superficial fissuring of the lips and scaling erythematous eczematoid dermatitis of the eyelids. In most patients, both lichenoid and eczematoid lesions are present. There is predilection for the legs, forearms, dorsal surface of hands and feet, face, V of neck, buttocks, genitalia, mucous membranes of the mouth, eyes, and eyelids. All the above manifestations are included under the term "atypical lichen planus." In addition, another syndrome occurs, a symmetrical eczematoid dermatitis, characterized by vesicular oozing plaques on hands, arms, feet, legs, and sometimes other parts.

Patients may develop acute exfoliative dermatitis secondary to any of the types mentioned.

**Treatment** consists in stopping the drug, hospitalization, and bland medications locally, such as 1:9000 *potassium permanganate soaks*, *Burow's solution soaks*, 5 per cent *aqueous tannic acid spray*, and *borated cold cream* if indicated. Sunlight and ultraviolet light are to be avoided. X-ray in small dosage is sometimes used. **Prognosis** varies, in general is excellent if treatment is instituted early. Recovery is, however, a matter of weeks or months. Residual hyperpigmentation, depigmen-

tation, and atrophy gradually show improvement.

Rare manifestations of atabrine toxicity may include the following: primary exfoliative dermatitis, urticaria, bluish discoloration of nail beds, hard palate, epiglottis, and tracheal rings, agranulocytosis, aplastic anemia, and severe acute hepatitis very occasionally, associated with the skin lesions. The mortality of the last two is close to 100 per cent.

Psychologic disturbances, toxic delirium, or brief periods of confusion in association with the use of atabrine are well known, especially with unduly large doses, but sometimes with moderate or even suppressive dosage. Usually symptoms disappear rather promptly when the drug is discontinued. Gaskill and Fitz-Hugh<sup>9</sup> report on 35 such cases seen in a total of 7604 malaria patients treated with atabrine in the U. S. Army 20th General Hospital in Assam, a 0.46 per cent incidence. The patients included six Americans and twenty-nine Chinese. Atabrine was being prescribed in a total dose of 2.1 gm. The time of onset of psychosis varied, the earliest being on the third day of treatment, the latest twelve days after completion of treatment. Some patients showed sudden increase in motor and psychomotor activity, with or without delusions and hallucinations. Others gradually developed confusion, disorientation and loss of recent memory, and became bewildered, fearful, and withdrawn. All but two of the patients recovered in eight to eighty-five days, the average period being twenty-three days. In the two who failed to recover, a schizophrenia had apparently been precipitated. Sixteen of the patients were later treated again with atabrine, without recurrence of symptoms except for mild excitement for one day in a single patient on the last day of treatment.

Undue emphasis must not be placed upon any of these toxic manifestations. Their incidence is low and the total disability caused not to be compared with that of unsuppressed and untreated malaria. Malaria itself may cause neuropsychiatric symptoms<sup>10</sup> often amenable to antimalarial therapy. Acute hepatic malfunction due to malaria is recognizable by liver function tests and sometimes clinically.<sup>11</sup> As a rule, it is promptly reversible.

It is well known that malaria at times produces false positive complement fixation reactions for syphilis. Studies have been undertaken by a number of workers in an effort to define the extent to which false positive reactions occur and their persistence. Study was made<sup>12</sup> of 100 soldiers with vivax malaria in first attacks or relapses, all with parasites in the blood. None of the patients had syphilis. Blood and spinal fluid examinations were made within five days after diagnosis. The Kahn test was employed and, when positive, was repeated weekly until negative. Spinal fluid, Kahn, and cell count were normal in every case. In two patients the Pandy test showed a "trace" of cloudiness. Blood serology was positive in 33 per cent, doubtful in 11 per cent. The number of previous attacks of malaria had no obvious bearing on the findings. Of those with positive or doubtful serologic tests for syphilis, 75 per cent became negative by the end of four weeks, 100 per cent in eleven weeks. Another study<sup>13</sup> of blood and spinal fluid includes 100 patients with malaria and without syphilis. Blood and spinal fluid were taken within forty-eight hours of hospital admission. Spinal fluids were all negative to Wassermann and Kahn tests. Colloidal gold tests were likewise negative. All spinal fluid cell counts were normal except one with seventeen cells, six polymorphonuclears,

and eleven lymphocytes. All other examinations in this individual were negative. Spinal fluid protein was normal in all but three patients in whom figures of 75 mg. per 100 cc. were obtained. The only other positive findings in these three were a doubtful blood Kahn and Wassermann reverting to normal in four days in one, and a positive blood Kahn reverting to normal in sixteen days in a second. Blood serology was positive in 12 per cent, doubtful in 10 per cent. Abnormal tests repeated at approximately weekly intervals all became negative within a month. Among these patients, 16 per cent of forty-nine from the Solomon Islands, whose infection had been present an average of seventeen months, had abnormal serology, and 29 per cent of forty-five from the Mediterranean and New Guinea in whom the infection had averaged nine months' duration. No definite conclusions are possible. The effect of vivax as compared with falciparum infections is unknown. One patient in this study had falciparum malaria. He had a positive serology. The whole question has been further investigated by Babin and Dulaney.<sup>14</sup> In 200 naturally infected patients with relapsing vivax malaria, 23.5 per cent developed a positive Wassermann, the largest number six to ten days after an attack. Among 408 miscellaneous sera with positive Kahn reactions, 14.5 per cent gave strongly positive complement fixation reactions for malaria, most of these being sera with high titer reaction for syphilis. In a third group of twenty-two patients with malaria induced for the treatment of syphilis, 82 per cent showed rise in the Wassermann titer along with the development and rise of a positive malaria complement fixation. Evidently false complement fixation tests for either disease may be induced by the other in a certain proportion of patients,

though the nature of the relationship has not been determined. Attempts have been made<sup>15</sup> to apply to malaria patients with positive serologic reactions for syphilis a full battery of tests to establish a pattern that will separate the false from the true. So far none of these can be regarded as infallible.

Opportunity has been offered in this war to see the initial impact of malaria infection in tens of thousands of young healthy previously uninfected persons and to follow them through their series of relapses. The experience at the Marine Barracks, Klamath Falls, Oregon, has demonstrated that most of the patients with relapsing vivax malaria are physically fit between attacks. Zeligs<sup>16</sup> comments on the fact that "postmalaria asthenia" is a misnomer in these individuals, though the term, "asthenia," is all too truly applicable in infected native populations in endemic and hyperendemic regions. In our troops with malaria, any early "asthenia" could usually be accounted for by the fatigue, hunger, strain, and fear associated with combat. A large group at Klamath Falls after at least three months' rehabilitation, showed negligible asthenia despite numerous recurrent attacks of malaria. Certain interval symptoms were attributable to uncured malaria, most commonly headache, which occurred in 15 to 20 per cent of the patients. The "typical" malarial headache is not "bursting" or "intense," is seldom over the vertex, is not described as "weight" or "pressure," is not unilateral and not associated with nausea or vomiting. It is a mild to moderate bilateral frontal headache, most often present in the morning on arising and improving after a few hours. The patients usually find that exertion, especially with exposure to the hot sun, brings on severe headache. Headache does not yield to the usual remedies but

was relieved in eighteen of twenty-five patients by nicotinic acid, 100 mg. by mouth. Such relief often lasted several days. Action on the cerebral circulation was thought responsible for the effect.

Nicotinic acid and its amide have also been used successfully in cerebral malaria.<sup>17</sup> In two patients reported, intravenous quinine was also given in small 4-grain doses. Response in the first case was satisfactory with return of consciousness in nine and one-half hours; in the second, more dramatic, the patient becoming conscious thirty-five minutes after the intravenous injection of one dose of quinine and 200 mg. nicotinic acid.

Many questions begin to arise in the United States concerning the probability of passing on malarial infection through blood donation. Despite careful screening of blood donors, there have been instances of transfusion malaria in the past and the opportunities for such accidents are considerably enhanced with the return of troops from malarious regions of the world. McClure and Lam<sup>18</sup> review the situation to date, mention the twenty-nine cases recorded in the literature up to 1938 and the fact that Gordon (1941) was the first to record a case of transmission by stored blood. In Gordon's case, the blood was two days old. The authors report two cases in which the stored blood had been refrigerated for five days. Both the patients were transfused during operation, with blood from Italian donors, born in Sicily, both of whom had lived in the United States for thirty years. The incubation period in the two patients was thirty-two and twenty-six days respectively. In both recipients, quartan parasites were found. Sharnoff and others<sup>19</sup> report two more instances, one of quartan malaria acquired a few days after three transfusions, the third donor being a veteran

from Africa where he had been hospitalized with chills, fever, and sore throat some months previously. His blood had been stored for eight days. In the second case, two-day-old bank blood from a Puerto Rican donor transmitted tertian malaria. This donor confessed to a "fever" two years before. The blood of both donors was negative on examination. Three other patients with transfusion malaria are said to have been seen in New York within a year. By way of contrast, the authors recall that Lozner and Newhouser succeeded in only one of thirty-five attempts to transmit the disease by plasma from patients with active malaria. Pertinent to this discussion is the report of Officer<sup>20</sup> from Australia on experimental transfusion with malaria-infected blood. Five healthy volunteers were each bled 750 cc. or until signs of collapse appeared and were then transfused with 560 cc. of citrated blood to which had been added an amount of malarial blood sufficient to contain 300 million parasites. Immediately after, antimalarial therapy was instituted. None of the volunteers developed malaria. The number of parasites injected was much in excess of such as would be transfused accidentally.

One concludes from our accumulating information that blood may readily prove a source of transfusion malaria even when stored for as long as eight days.

Since transmission of malaria is possible decades after the infection and since persons harboring malaria parasites may have forgotten or never have known that they had the disease, those who have lived or traveled in the tropics or known malarious regions had best be refused as blood donors. An exception might be considered if blood is to be used as plasma. If, as an emergency measure, blood is used where doubt regarding malaria exists, a course of antimalarials

following the transfusion should protect the patient.

Malaria may, of course, be dangerous to a debilitated patient. Apart from that, however, transfusion malaria is comparatively benign as it runs a very different course from the naturally acquired disease. In transfusion, malaria relapses are not anticipated after the original attack has been adequately treated. Almy<sup>21</sup> reports that in his study of about 200 cases of therapeutic malaria induced by intravenous injection of malaria-infected blood, treatment with quinine or atabrine has cured the disease in all with no relapses. Absence of a tissue phase when trophozoites instead of sporozoites are injected could explain the difference.

Concern has been expressed as to the effect in the United States of importing into this country large numbers of patients with relapsing malaria acquired during their military service in the tropics. Several laboratory experiments have been arranged to give American mosquito vectors opportunity to bite these patients with foreign malarias. It is proved that malarias from the Southwest Pacific, the Mediterranean and elsewhere are infective to our native mosquitoes, *A. quadrimaculatus*, *A. maculipennis freeborni*, and others. Further, these mosquitoes, thus infected, were found capable of transmitting the disease to uninfected volunteers.<sup>22-24</sup> Such transmission has also occurred in nature resulting in one small secondary epidemic traced to a veteran. The report<sup>25</sup> is that of a returned soldier with relapsing vivax malaria, who lived in a tent for some weeks in a malaria-free county in Oregon, where he was responsible for passing the disease on to two persons in nearby houses and probably to his partner as well, though the latter could not be traced.

It is important to be on guard against the spread in the United States of imported strains of malaria. However, secondary epidemics are unlikely to be frequent or extensive and will, in the main, be naturally controlled by factors already in operation in regions at present free from malaria. The question is different in our endemic regions in the south and southwest. Here imported and native malarias should be regarded as one problem, and attacked vigorously with the new methods and new insecticides now at our disposal. From a practical point of view, emphasis should be placed on mosquito control rather than on limiting the freedom of infected persons.

### Scrub Typhus

The disease known as scrub typhus or tsutsugamushi occurs in parts of India, Burma, Assam, Indo-China, and Thailand, Malaya, Sumatra, Java, Borneo, the Celebes, the Philippines, New Guinea, New Britain, Bougainville, New Georgia, Santo Espiritu, and Australia, as well as in Japan, Formosa, the Pescadores, and the Ryukyu Islands. Knowledge of its distribution has been acquired in part by the experience of our troops, among whom extensive epidemics have appeared in unexpected places. "Typhus islands" of spotty distribution have been known to be present in many of these areas. They have been largely "silent," however, until troops entered and to their cost became unwilling "indicators" of the presence of the disease. Nearly 3000 cases of the disease occurred in one three-month period during a series of operations in the South Pacific. Mortality varied greatly, from 1 per cent in two epidemics in New Guinea to 30 per cent in the small epidemic of forty to fifty cases on Goodenough Island. At one period scrub typhus was found to be the only disease that was killing sol-

diers in numbers in the South Pacific. The U. S. Typhus Commission sent a group of investigators to New Guinea to work on the problem in 1943 and 1944. They studied the situation in northeast New Guinea and certain nearby islands and have reported their findings.<sup>26-29</sup> They proved the identity of the disease with tsutsugamushi of Japan by isolating rickettsial strains from patients and producing typical pathologic lesions in inoculated mice and hamsters from which, in turn, typical rickettsiae were recovered. Efforts were made to work out the epidemiology in the islands. Small mammals, especially rats and bandicoots, were collected along with their parasitic mite larvae. Other mite larvae were collected by the simple expedient of sweeping up those that crawled onto the boots of anyone standing still in a mite-infested area. After identification, pools of mite larvae and organs of mammals were injected into laboratory animals. *Rickettsia orientalis* was recovered from two species of mite larvae, *Trombicula delienses*, and *T. fletcheri*, the former long suspected as a vector in Malaya, but hitherto without proof, the latter possibly a variant of *T. akamushi*, the known vector in Japan. One mammal, *Rattus rattus concolor*, was identified as an infected host. Scrub itch mites were plentiful but apparently have no connection with the disease. Some explanation is arrived at for the great difference in attack rate in epidemics, the highest being that on Bat Island, where 60 per cent of the personnel came down with the disease before the island was abandoned. Investigation there by commission members, who went in warily with impregnated clothes, showed an enormous mite population infesting a large rat population all confined to the small island. Elsewhere, infection was found to be taking place especially in

certain bivouac areas and where camps were being established. The maximum danger was in the first two weeks and danger was minimal after four to five weeks. Development of a site apparently drove out the vectors. In many places, kunai grass fields were danger spots. The habits of the vector were observed. Larval mites bite either day or night. The position of the eschars, many times on the upper part of the body and even the face, suggests that soldiers were bitten often as they sat or lay down. The mite larva requires one feed of tissue fluid from a warm-blooded animal and when it bites, it stays attached three to five days. If it is removed or if its host dies before the feed is completed, it has not been found to bite another host.

The unexpectedness of these epidemics of scrub typhus was partly due to the absence of epidemics in native populations. We find a record in some places, however, of a 70 per cent infection of natives before the age of fifteen. Under these conditions, immunity in the adult natives might be expected.

So far, protective vaccine is not available against scrub typhus. Epidemic typhus vaccine offers no cross protection. Available methods of prophylaxis are twofold: reduction of mites and individual protection by repellents. When an area is to be entered, it should be prepared by using native labor where possible to cut and haul away or burn scrub growth and grass at the site. The site is then treated thoroughly by bulldozer or burned over by flame thrower. Troops should not sleep on the ground. The second means of protection is the issue of clothing impregnated with 5 per cent benzyl benzoate to all troops entering infected areas. Trouser legs should be tucked into socks and high boots worn.

Symptoms of scrub typhus are similar in most respects to those of epidemic

typhus. The incubation period is commonly nine to ten days (range seven to eighteen). The rash is a typical rickettsial rash, macular or maculopapular, and may extend to wrists and ankles or even to the face. The death rate is comparatively high in patients over forty. Headache, malaise, anorexia, conjunctival congestion, aches and pains in neck, back, or limbs, and temporary deafness are common symptoms. Only the new observations will be stressed in the reviews to follow.

Sayen, Pond, Forrester, and Wood<sup>30</sup> report on 616 patients with scrub typhus contracted in the Assam-Burma area, hospitalized in the 20th General U. S. Army Hospital in Assam. Illness tended to be more severe and mortality higher among groups of patients who contracted the disease after weeks of jungle combat on short rations, or when they were compelled to continue marching or fighting after the onset of disease. Mortality ranged from 0 to 16 per cent, averaged 5.2 per cent for the 553 patients acutely ill on admission. Two hundred patients were studied in detail and further statistical data are based on this group.

Clue to early diagnosis was a knowledge of the patient's whereabouts one to three weeks before the onset, but early definite diagnosis was possible only on finding a typical primary lesion. The patients often discovered the lesion one to fourteen days before onset of the disease. Thorough search over the whole body was necessary with the fact in mind that on moist surfaces the typical black crust and red flare might be absent in the initial lesion. The lesion was found in 60 per cent, and glandular enlargement with tenderness in 30 per cent of those with the lesion. Generalized lymphadenopathy, usually with some tenderness, occurred in 97 per cent of

patients. Typical rickettsial rash appeared about the fifth day (third to seventh). Weil Felix OXK agglutination became positive in 1:100 titer in only 50 per cent of patients, and never before the tenth day. A titer of 1:100 was thought significant as this titer was never found in normals nor in other diseases. (Note: Other workers regard 1:160 as significant.) Maximal titers, occasionally 1:6400, were reached in the third or fourth week and thereafter declined. Titers were seldom significant after eight weeks. OX19 and OX2 agglutination titer never exceeded 1:50.

Fever lasted five to thirty-six days, was irregular, usually with double daily spikes at some period of the disease. Pulse rates tended to be comparatively slow.

Leukocytes were usually normal or low the first week, rising often in the second or third weeks, occasionally as high as 20,000, with concurrent rise in the polymorphonuclears. In all survivors, the absolute lymphocyte count rose after the tenth day. Sedimentation rate usually rose about the third week and remained elevated as long as two months in some. Albuminuria was present in most patients, often with coarse granular casts, sometimes with a few RBC. Twenty-one per cent of patients had fixed specific gravity in the late second or third weeks, sometimes with oliguria and a rising blood urea nitrogen, especially in the more seriously ill. Subsequent diuresis proved a good omen. Serum proteins were reduced below 6 gm. per 100 cc. in two thirds of the patients.

Eye examinations were carried out in a group of 451 patients weekly during their illness and continued on into convalescence. There was conjunctival injection in 38 per cent in the first



week, subconjunctival hemorrhage in 6 per cent, hemorrhage of the eyelids in 1 per cent. In the first or second week, 67 per cent of patients had marked engorgement of the retinal veins which then became tortuous and showed a blurred outline, accompanied by similar but less marked blurring of the arteries. Edema of disk and retina then appeared in 36 per cent of patients. Disk swelling was mild, never over 2.5 diopters. It was regarded as due to local inflammation. Retinal hemorrhage appeared in 6.6 per cent, exudates in 5 per cent, at the height of retinal edema. This retinopathy was not seen in other diseases and made the diagnosis in several patients a week before a positive Weil Felix reaction was obtained. The retinopathy appeared on the tenth to seventeenth day, disappeared during the fifth to eighth week. (*The Reviewer notes that ocular findings in epidemic typhus in many respects similar to these have been reported by Müller,<sup>31</sup> who found 78 per cent of 125 patients with dilated retinal veins, retinal hemorrhages in 14 per cent, macular changes with edema in 42 per cent, with an additional finding of specific nodular infiltrations of retina or choroid in 28 per cent.*)

In the first week of the disease, it was impossible to tell whether the case would be severe or mild, hence all patients were kept at strict bed rest from the first moment. At any time after the first week, certain phenomena indicating major organ dysfunction might occur and were signs of danger. Severe rickettsial pneumonia, of dangerous degree, was recognized by cyanosis of the skin and/or tachypnea. Physical signs and x-ray findings were less helpful in diagnosis. Dangerous degrees of meningoencephalitis were often recognized clinically. Meningismus, delirium, convulsions, and coma were danger signals. On the other

hand, rickettsial myocarditis was not recognizable clinically as it did not produce congestive heart failure and, though ultimately disastrous in certain patients who developed pulmonary edema terminally, danger from this cause was never predictable. In the absence of other diagnostic characteristics, the diagnosis of scrub typhus should be suspected in any patient with fever who gives evidence of multiple organ dysfunction, especially persistent muscular twitchings and marked increase in respiration rate with few signs of consolidation.

The prognosis was always fatal in a patient whose cyanosis was unrelieved by oxygen, or who had persistent hyperpnea, pulmonary edema, or coma lasting twenty-four hours.

**Treatment**—In therapy, rest, adequate nutrition and fluids, and good nursing were the essentials. In dangerous illness, three other measures were available: oxygen, transfusions, and heroic sedation, used on indication. **Penicillin** and transfusions of immune blood or plasma were ineffective.

Convalescence is a critical time with these patients both physically and psychologically, as three to four months are often required. However, 75 to 85 per cent of the patients should be able to return to full duty within that length of time. All mild and moderate cases and many of the serious ones can be gradually but firmly guided toward normal living and then into increasing activity. Symptoms in convalescence are not, as was at first feared, due to myocarditis but are mainly those of effort syndrome, the result of general weakness with an associated psychoneurotic element.

Specific forms of treatment for scrub typhus are under investigation. Topping<sup>32</sup> has prepared immune rabbit serum which will save mice injected with otherwise certainly fatal doses of

involvement of scrotal contents or of superficial lymph vessels and nodes in arm or leg. First sign was often acute epididymitis; most frequent sign, acute funiculitis. Involvement of superficial lymph nodes and vessels was much less frequent and was associated with pain, tenderness, and swelling. If in the arm, axillary nodes were first affected, later epitrochlear. A wide red raised tender cordlike streak might extend from axilla to elbow along the inner arm, occasionally the whole length of the arm. Such symptoms usually required hospitalization, partly subsided in a week or two, allowing the patient to become ambulatory, and disappeared in another few weeks. This same chain of events in the inner thigh started from nodes in the groin. In an occasional patient, cellulitis appeared beneath the biceps or in the inner thigh, tending to become a burrowing abscess with pockets. At times, arm, hand, leg, or even the upper eyelid were sites of soft nontender swellings without signs of inflammation. Multiple occurrence and transiency were here the unique diagnostic characteristics. Fever was notable only when acute cellulitis or lymphangitis was present. Retrograde lymphangitis, lymphadenitis, and lymphedema as described form the triad of symptoms characteristic of the disease. The course of the disease was marked by intervals of freedom from symptoms followed by recurrences after one to three months. A hundred patients were examined by thick blood smear for microfilariae with negative results.

In this same island region, the authors studied endemic filariasis in the native population for comparison. Forty per cent of 100 natives examined had microfilariae in the blood. A much larger proportion was doubtless infected. The microfilariae present showed no periodicity in their appearance. Natives of all

ages showed signs of the disease, but microfilariae are not found in children under three to five years of age. Lymphadenopathy was very common in the chronic native infections. Elephantiasis was present in an estimated 5 per cent of the population, in people in their twenties and thirties and up to old age. Few were incapacitated by it. Thighs and legs were chiefly affected, the scrotum often in males, and the breast in females.

Acute manifestations as seen in American soldiers rarely appeared in natives, who have apparently acquired some degree of tolerance. In natives, acute exacerbations of a different type, so-called "filarial fever," occurred in attacks, with severe generalized aching, chills, prostration, and fever sometimes to 103° F., the whole attack lasting only three to four days. The peculiar abscesses described in a few Americans were found in many of the natives and among several hundred treated one filarial worm was found in the pus.

The epidemiology of the disease as related to American troops is a fascinating story. The chief, if not the only, vector of the disease in the Samoan area is *Aedes scutellaris pseudoscutellaris*, a day biter.<sup>41</sup> It is frequently found infected with larvae in the infective stage in and near native villages but a few hundred feet away there are no infected mosquitoes. The facts recounted by Englehorn and Wellman<sup>40</sup> indicate the close relation of native infection to epidemics in the troops. In their own hospital, only fifty yards from a native village, members of the hospital unit developed the disease at the rate of 50 per cent a year; in a service unit several hundred yards from native villages, the rate was 28 per cent; and in a group of units five miles away, 6 per cent.

Night-biting mosquitoes were evidently not responsible, for all troops had contact with the natives after sundown at movies and dances and in the villages, yet the rate of infection was not thereby equalized.

The absence of true epidemics of filariasis among troops except in Samoa and the nearby islands in the South Central Pacific is difficult to explain as the disease is endemic among natives throughout both the South and the Central Pacific area.<sup>42</sup> Factors concerned are thought to be related in part to a difference in vectors but complete explanation is not yet apparent.

The obvious preventive measures include mosquito control and segregation from the natives. Where such measures are impossible, the period of exposure must be limited to a minimum.

Thompson, Rifkin, and Zarrow<sup>43</sup> report their clinical observations and laboratory findings in 200 young soldiers with filariasis and describe changes in pathology noted in biopsy material as the disease grows less acute. All their patients had enlarged lymph nodes, larger and softer and usually tender in the acute stages. They found an intradermal test employing 0.05 cc. of a 1:4000 dilution of an antigen made from *Dirofilaria immitis* specific (except in one instance) and uninfluenced by intestinal helminths. Eosinophilia was present in 34 per cent of the patients but seldom highly remarkable, the average count being 10 to 15 per cent, the highest 25 per cent.

**Treatment**—Methods of treatment are few and simple, rest during the acute attacks, and in the very early stages limitation of activity between attacks. After the first acute period, increase to normal activity is important even though such activity may have to be halted briefly when recurrences appear. Drug therapy

is still in the experimental stage but promising results are being found in trial of the pentavalent antimony compounds.<sup>44</sup> Perhaps, above all else, it is important to deal with the patient's fears at the start. Impotence and sterility are disabilities that he fears and assurance that these fears are groundless is an important part of treatment. The fear of elephantiasis at some future date can be dismissed also on quite substantial grounds, including our recognition that natives in the endemic areas, heavily and continuously exposed from birth, develop elephantiasis in only about 5 per cent of the population and seldom under the age of twenty, that is, after twenty or more years of exposure.

Coggeshall<sup>45</sup> has made observations on many hundreds of men with filariasis at the Marine Barracks at Klamath Falls, Ore., and has been able to follow the course of the disease for months. He finds filariasis a mild disease, as it exists now in service men. The recurrent attacks of lymphedema, lymphangitis, and muscle soreness grow less frequent and will probably vanish completely in the course of a year or so. The attacks are temporary and no permanent swellings were observed in hundreds of cases followed over a period of eight months. No microfilariae were ever found. Lymph node biopsies have sometimes shown adult worms with microfilariae *in utero*, sometimes dead worms degenerating or calcifying, evidence that the body was eliminating the infection. (*Note—Biopsy has served a useful purpose in the past, and has even been used for diagnosis in the early epidemics. It is now not necessary for diagnosis and is not recommended.*) No fear of transmission of filariasis in the United States by returning service men need be entertained.<sup>46</sup>

### Schistosomiiasis

Infection with *Schistosoma japonicum* on Leyte was not unexpected as the island was known to be an endemic center of the disease. Several thousand men acquired the infection there.

A clinical description<sup>47</sup> of forty-two of the early proved infections includes certain combinations of symptoms found suggestive of the diagnosis even before ova appeared. These were fever, headache, anorexia, weakness, cough, pain in the chest, abdominal pain, and a tender liver with a white blood cell count over 20,000, and an eosinophilia over 40 per cent. In all these patients there was a history of exposure but only one had "swimmers' itch." Onset was insidious in twenty-four patients, abrupt in eighteen with a first complaint of urticaria in seven. Abdominal pain was either that of a tender liver or, more characteristically, the generalized, shifting pain after meals or at night, unrelieved by the usual sedatives, due to intestinal irritation from the parasites. Diarrhea was uncommon. Fever was usually present (thirty-three patients) in the afternoon and evening, with profuse sweats as the temperature fell. Fever lasted one to thirty-three days and usually disappeared the third or fourth week regardless of treatment. In twenty-six patients there was early dry hacking cough, disturbing at night, later becoming productive. Eleven patients had chest pain, three had scattered râles. The most constant sign was a tender palpable liver present in thirty-eight patients. The spleen was palpable in seven.

Laboratory findings were most significant: WBC, 20,000 to 50,000 in twenty-nine, 15,000 to 20,000 in nine, 10,000 to 15,000 in four; eosinophilia above 50 per cent in all but nine, in these nine averaging 40 per cent. (Note—

Others report eosinophilia up to 90 per cent.) X-ray changes in the lung were found in twelve patients, in seven as diffuse, rather uniform mottling throughout, and in the other five as areas of consolidation in the bases similar to those of bronchopneumonia. All twelve had increased linear markings as well.

Sigmoidoscopy in thirty-five patients showed no abnormalities in twelve, while twenty-three had characteristic multiple small firm yellow nodules, 1 to 3 mm. in diameter, occurring in clusters of three to twenty-five beneath the mucosa. They were most abundant at the rectosigmoid junction but were seen also above and 4 or 5 cm. distal to that site. There was no associated ulceration or inflammation and no relation to visible blood vessels. Biopsy showed many ova, some immature beneath the mucosa. These nodules are pathognomonic. They have been described in dogs, never before in man. They may be present before ova can be found in the stools.

Symptoms, signs, and blood picture all improved and all stools were negative twenty days after starting therapy.

Of particular interest in this series were two patients with neurologic symptoms. One had minimal symptoms, evidence of a minute lesion in the pyramidal tract. The second was a twenty-three-year-old white soldier admitted January 9 semistuporous. He had fought through rice paddies, swamps, and streams in Leyte October 20 to December 1, 1944. Illness started December 19 with gradually increasing weakness and fever. By January 8 he could hardly use his arms and legs and the next day his limbs were completely paralyzed and spastic, with increased reflexes, clonus, and bilateral Babinski. Temperature was 101° F. and he was disoriented and incontinent. There were no sensory changes. Blue discoloration of each small toe and plan-

tar surfaces of the others indicated embolic occlusion though vessel pulsations were present at the ankle. Spinal fluid was normal twice. Leukocytosis of 27,000 and 35,000 with 38 and 54 per cent eosinophiles suggested a diagnosis of generalized schistosomiasis. A week after admission, foudadin therapy was started. The same day ova were found in the stools and on February 5 characteristic nodules were observed on sigmoidoscopy. On February 9 he could sit up. February 19 he was evacuated walking. Twenty-odd patients have been seen subsequently in the United States in whom neurologic symptoms were attributable to deposition of ova in the brain. Among them were two patients reported by Faust<sup>48</sup> with symptoms of brain tumor, one of whom died, the other being operated upon with successful removal of a large granulomatous tumor which had formed about deposited ova. Symptoms of jacksonian epilepsy have appeared in some patients and one patient was confined as a psychopath for a time. Further evidence of the widespread distribution of ova was observed in a patient (mentioned by Faust) who presented subcutaneous nodules about the chest which on biopsy were found to contain ova. This has previously been recognized in *Schistosoma hematobium* infection.

Though the only sure proof of diagnosis is the finding of the characteristic ova, yet in patients who have been exposed in endemic areas and who develop, in three to four weeks or less, itching, urticaria, fever, a dry cough, and increasing eosinophilia without other satisfactory explanation, the presence of schistosomiasis may be regarded as probable.<sup>49</sup>

No new methods of treatment have been developed. *Tartar emetic* in a total dosage of 1.8 gm. or *foudadin* in a total dose of 75 cc. is recommended.<sup>50</sup>

The epidemiology of schistosomiasis on Leyte is fairly clear. Intermediate hosts are the snails, *Schistosomophora* (*Oncomelania*) *quadrasi*. The number of snails infected ranged from 0 to 21 per cent in a study by Magath and Mathieson,<sup>51</sup> varied even at two ends of the same swamp, dependent on native habits of defecation. Pigs and dogs are found 100 per cent infected with schistosomiasis in regions of high endemicity, and they contribute to infection of the snails. Infective cercariae emerging from the snails are fragile and short lived. They die in about forty-eight hours. They do not move far but may be washed along by currents for a mile or so. Scattered, broken, or largely diluted by the time they reach a large or swift stream, they can scarcely be numerous enough to infect a swimmer with the 100 probably needed (by analogy with experimental animals) to produce clinical infection. Hence reports of an infective swim in a large river are probably erroneous; more likely is it that splashing through the swamps adjacent to a village has been the infecting contact. In endemic regions, human infection may run very high, in one such region 50 per cent of five-year-old children and 75 per cent of ten-year-olds being found infected on a single stool examination. Determination of the endemicity of an area may be accomplished by examining stools of the native inhabitants for ova, or finding infected snail hosts. Still simpler is the demonstration of infection in trapped wild rats from localities in question.<sup>52</sup>

Infection of man with *Schistosoma* may occur through the skin or mucous membranes. Chlorination is found to kill infective cercariae of *S. mansoni*<sup>53</sup> and will probably kill those of *S. japonicum* as well. Chlorination could not, however, be depended upon in natural bodies

cured cases of amebic dysentery is reported much more frequently from India and from England (much of it acquired abroad) than from American experience. Payne<sup>61</sup> reports 1000 proved cases of amebic dysentery in two years' experience in India. Of these, 50 per cent had mild hepatitis, 3.9 per cent acute amebic hepatitis, and 2.8 per cent, hepatic abscess. *Emetine* injections, followed by *carbarsone* for ten days brought about clinical cure in 50 per cent or less. Within three weeks, 40 per cent were showing cysts. By contrast, we find Browne<sup>62</sup> and others summing up results in 790 patients with amebiasis treated with various drugs, with a total of only fifty recurrences, patients being considered cured when asymptomatic for three months with three negative stool examinations. Similarly, we find chronic recurring or relapsing dysentery little of a problem among approximately 500 American soldiers treated for amebic dysentery in Assam (U. S. Army 20th General Hospital).<sup>63</sup>

Destruction of amebic cysts in drinking water is always a more difficult matter than elimination of bacterial contamination. Boiling for one minute is adequate. Comparatively high chlorination will be effective, 2 p.p.m. residual after thirty minutes' contact for relatively clear water.<sup>64</sup> When lettuce and other raw foods are to be cleansed, certain detergent chemicals have been investigated<sup>65</sup> and found acceptable. For the best of these, the cysticidal dose was about 30 p.p.m. for ten minutes. (*Note*—Ceepryn may be used at 50 p.p.m. for thirty minutes.) The best substances studied were Fixanol (duPont), Sapamine (Ciba), Nopco QCL (Winthrop), and Ceepryn (Merrill). Medical men returned from overseas report "mikroklene" as being useful for similar pur-

poses at a level of 3 to 5 gm. per liter with contact for thirty minutes. These chemicals are not to be used in drinking water.

Röntgenologic findings in amebiasis are reported in two papers. Golden<sup>66</sup> reviewed the findings in 119 patients with proved or suspected amebiasis (107 with *E. histolytica* in the stools). Thirty of the sixty-seven who were x-rayed had deformity of the cecum, twenty-one of them proved cases of amebiasis, the other nine neither proved nor disproved. He finds that recognizable deformity of the cecum is likely in over one third of cases of amebiasis and still more likely if the patients have intestinal symptoms, especially diarrhea (eighteen of thirty-three patients with diarrhea in their study). In a number of cases, such x-ray finding has been the first evidence pointing toward amebic infection. The x-ray findings are those of cecal deformity, often only slight, and usually smooth. Often size and outline changed a little during examination. There was usually localized tenderness. The terminal ileum was never intrinsically deformed, an important point in differential diagnosis. Flexible narrowing or irregularity of the wall distal to the cecum may be considered additional evidence of the diagnosis.

Druckmann and Schlorr<sup>67</sup> stress the necessity for making a diagnosis in case of amebiasis of the large intestine before surgery. They have seen a gastrectomy for duodenal ulcer followed by death from fulminating liver abscess, and another death following the usually benign operation of colostomy, in this case carried out for obstruction, which proved to be an amebic stenosis. They outline differential diagnosis from carcinoma as dependent on (1) a relatively long area of gut involved; (2) multiplicity of lesions

often; (3) incompleteness of narrowing; (4) slight or absent pain on distention; (5) gradual merging of defect into normal contours; (6) incomplete loss of elasticity; (7) incomplete loss of normal relief pattern; (8) complete or partial restoration after specific therapy.

### Bacillary Dysentery

Hardy<sup>68</sup> describes results in 1423 persons with *Shigella* infection treated with **sulfonamides**. Cultures were taken before, after, and daily during treatment. In 382 Flexner cases or carriers, only absorbed sulfonamides were used, all highly efficacious in ordinary dosage, the last positive culture being on the fourth day. Two gm. daily gave as good results as 4 gm. In outbreaks of Schmitz infection with 246 patients, results were a little slower and response to **sulfathiazole** and **sulfaguanidine** comparatively poor. Seven hundred ninety-five cases or carriers with Sonnei infection were treated, 621 of them in one outbreak. Nineteen per cent of these patients had organisms persisting more than seven days. Response was slower than in either the Flexner or Schmitz group. Complete clearing was obtained in all cases given **suxidine** but some responded to no other **sulfonamide**. With the absorbed drugs, a 4-gm. daily dose was better than 2 gm. One hundred thirteen of the Flexner cases were followed for two months after treatment with an average of eleven cultures per person. None had recurrence. Seven Shiga strains were tested *in vitro* and responded in similar fashion to the Schmitz strains, less well than Flexner, better than Sonnei.

The conclusion is reached that three **sulfonamides** are superior to the others, **sulfadiazine**, **sulfapyrazine**, and **sulfasuxidine**. **Sulfadiazine** is recommended as the drug of choice for Shi-

gella infection with later substitution of **sulfasuxidine** in cases that respond poorly.

Incidence of *Shigella* species in the various theaters of war is of some interest. MacLennan,<sup>69</sup> working in the Central Pathology Laboratory for the British Middle East Forces, 1940-42, received cultures of all strains inagglutinable in other laboratories. He found that most of 217 doubtful strains belonged to the Sachs types (nonmannite fermenters other than Schmitz and Shiga, recently studied by Sachs). Among all the cultures identified in his laboratory, these types accounted for 1.7 per cent. They proved to be antigenic in rabbits and all but one serologically distinct. He regards the case for their pathogenicity as being very strong since they were found only in patients with dysentery or diarrhea and occurred (in 90 of 119 cases) in patients passing stools with typical bacillary dysentery exudate.

Incidence of *Shigella* species is reported by Fortune and Ferris.<sup>70</sup> Among 2849 patients with diarrhea admitted to an Australian general hospital in New Guinea, over eighteen months, 36 per cent had proved bacillary dysentery, 1.4 per cent amebic dysentery. Randall and Dunn<sup>71</sup> found 426 proved *Shigella* cultures among many sent in to a U. S. Army laboratory in Algeria from a number of units during a fourteen-month period, June, 1943, to August, 1944. Heinemann<sup>72</sup> in Egypt obtained 288 *Shigella* organisms on culture of 3078 stools of United States military personnel suffering with illnesses suggesting dysentery, diarrhea, or enteritis during the period October 1, 1943, to August 1, 1944. Comparison of the four reports indicates the scarcity of Shiga and prevalence of Sonnei infections in United States as compared with British figures.

soldiers being vaccinated against smallpox. They found 51 per cent of eighty men with vaccinia and 34 per cent of forty-nine with vaccinoid types of response to have doubtful or positive reactions for syphilis. These reactions did not develop immediately. The optimum time for their discovery was ten to twenty-one days after vaccination. Most had disappeared at the end of three months.

Improved results in treatment of smallpox by the addition of *sulfonamides* (*sulfapyridine*) are reported by Osborne,<sup>83</sup> who finds toxicity and edema reduced and the usual purulent bronchitis prevented by its use.

### Kala Azar

It has long been known, Rose<sup>84</sup> says, that autoagglutinins, or cold agglutinins, are commonly present in the blood of both humans and animals with trypanosomiasis. He examined the blood sera of two patients with kala azar. In each case the serum was tested against the patient's cells and the cells of a normal person. Cold agglutinins were present in both patients at titers of 1:128 to 1:1024. In one of the two, the test was repeated and it was found still at its previous level of positivity two months after completion of treatment and discharge from hospital though the patient was well and the spleen no longer palpable. Seven weeks later it was practically negative. We do not know the cause or significance of these findings nor in what percentage of patients the test is positive.

Shortt<sup>85</sup> describes results of a complement fixation test for kala azar in 920 cases. The test originally employed an antigen made from human tubercle bacilli but more rapidly growing bacilli (Kedrowsky's bacilli) are now substituted. The test was positive in 93 per

cent of proved kala azar, doubtful in 6 per cent, negative in 1 per cent. It may be positive in some cases of only three weeks' duration, at a time when no other serum tests have become positive. Among a group of patients with other diseases likely to be confused with kala azar in differential diagnosis, 99 per cent had a negative complement fixation, 1 per cent doubtful. A few cases of obvious chronic pulmonary tuberculosis give positive tests.

We are now on the road to controlling the most classical and fatal complication of kala azar, according to Sen Gupta and Chakravarty.<sup>86</sup> Cerebrum oris, a complication with a 50 per cent or higher mortality rate in some groups of patients, was found in six cases treated by the authors to respond remarkably to combined intramuscular and local *penicillin* therapy. Routine treatment with *pentavalent antimony* was carried out coincidentally. Progress of the local lesions was very unlike the usual course. There was no extension. The slough separated in about seventy-two hours in five of the patients; the foul odor was gone in seventy-two hours; fever started to drop within twenty-four hours and was normal within a few days.

### African Trypanosomiasis

An extensive piece of work has made possible follow-up reports in 1800 of 2000 patients treated for trypanosomiasis over a year before. The 1800 were seen and examined and about 1000 had a lumbar puncture on reexamination. Harding<sup>87</sup> finds ten cells or less in the spinal fluid consistent with a cure and believes the cell count a more reliable indication than the protein level. He found four of the patients with reinfections, and one with a relapse. The treatment of this group had demonstrated high toxicity for one of the treatment schedules em-



ployed: Three doses of *antrypol*, 1 gm., followed by three to five doses of 2 gm. *tryparsamide*, all at five-day intervals. A delay of three weeks after the first dose of *antrypol* was found to reduce toxicity greatly, apparently by allowing recovery in the patient's general condition. By the best *antrypol tryparsamide* combinations, a cure rate of 93.5 per cent is obtained. The author draws attention, however, to the greater responsiveness to treatment of this Sierra Leone trypanosomiasis as compared with that in certain other regions.

Results in the early stages of sleeping sickness from the use of two new arsenicals, *melarsen oxide* (a trivalent arsenic oxide) and "70 A" (a phenylarsenoxide) are considered hopeful by Weinman and Franz.<sup>88</sup>

### Penicillin in Tropical Diseases

The usefulness of *penicillin* in certain tropical diseases not already discussed may be mentioned briefly.

In the spirochetal group of diseases, penicillin has been found extremely useful. In yaws,<sup>89</sup> it is very effective even in small dosage. Optimum methods of employing the drug in this disease are still to be worked out. Kahn reversal is not accomplished as early as are clinical results. In rat bite fever,<sup>90-92</sup> due to either *Spirillum minus* or *Streptobacillus moniliformis*, penicillin has proved curative. Relapsing fever is responsive to the drug. In Weil's disease<sup>93</sup> in mice, penicillin is found effective if used early. Results in humans are still in doubt.

The effectiveness of penicillin in actinomycosis and in anthrax with or without bacteremia is well recognized. Reports on its use in human bartonellosis<sup>94</sup> are encouraging. *Penicillin ointment* has been successful in hastening the healing of certain tropical ulcers.<sup>95</sup> In trachoma results with penicillin locally<sup>96</sup> have been

found equal but not superior to those obtained with *sulfonamides*.<sup>97</sup>

### Insecticides and Repellents

**Insecticides**—No discussion of tropical medicine could omit reference to the new insecticides and repellents for use against disease vectors. Outstanding among these is DDT (*dichloro-diphenyl-trichloroethane*), whose most remarkable property is a residual insecticidal effect when applied at certain dosage levels. Its early promise in the laboratory has been fully borne out in the field. Control of the Naples epidemic of typhus in early 1944 is unparalleled in the history of epidemics and is in striking contrast to our inability after the first world war to control a scourge of typhus that cost millions of lives in Eastern Europe. This was the first time in history that a typhus epidemic, once started, has been stopped in midwinter. An epidemic with approximately 1000 new cases in January was tapering off by March. Credit goes partly to the new insecticide and partly to the practical methods developed for using it that permitted the delousing of civilians without removal of clothing at the rate of 5000 persons an hour or 70,000 a day at the peak. DDT as a 10 per cent dust was applied by power dust guns inside the clothing, sleeves, neck, and belt, into hats and over hair. One and one-half ounces of the dust per person was needed and was effective in killing lice and, more surprising, in preventing reinfestation for weeks. The sordid living conditions among the population at the time actually enhanced the residual effect in that change of clothing with consequent wastage of the chemical was not possible. Armies can be protected in advance against typhus by vaccination; it is in the realm of civilian relief that DDT claims its greatest successes against the disease. Against

fleas DDT has been put to use in the control of plague epidemics in Algiers. Some of its most remarkable results, however, have been obtained in mosquito control. During the Italian campaign, DDT was sprayed from planes in a 2 to 5 per cent solution in kerosene in swaths 115 x 700 yards along the terribly infested Southern Po valley. As a result, mosquitoes and flies became almost non-existent and troops were kept relatively free of malaria.<sup>98</sup> In one of the Marianas in the first thirty days after occupation, 42,000 medical treatments were given 17,000 natives, of whom 508 died. Three months later, after insects were reduced, the deaths had dropped to 50. Angaur when occupied had a dengue epidemic going, yet thirty days after invasion, not a single case was found among the invading forces.<sup>99</sup>

Instances could be multiplied to show the significant rôle played by DDT in military campaigning. The United States Army has been supplied with DDT in a number of forms for a variety of uses.<sup>100</sup> Some of these are listed as follows:

1. Ten per cent DDT in pyrophyllite powder.
2. Five per cent DDT in kerosene (with or without 15 per cent methylated naphthalene as auxiliary solvent).
3. Twenty-five per cent DDT concentrate, with 10 per cent emulsifier (Triton X-100) and 65 per cent xylene. For use this is diluted with 11 parts of water to give a 2 per cent emulsion.
4. Three per cent DDT in an aerosol, 85 per cent freon — 12, with 2 per cent pyrethrum extract (20 per cent), 5 per cent cyclohexanone, and 5 per cent hydrocarbon oil.
5. One per cent DDT with 2 per cent thanite in kerosene.
6. Six per cent DDT concentrate with 68 per cent benzyl benzoate, 12 per cent benzocaine, and 14 per cent wetting agent. For use this is diluted with 5 parts of water to give a 1 per cent emulsion.

DDT, in one or more of the forms 1, 2, and 3, can be used effectively against

most insects and some arachnids. It is effective against mosquito and louse larvae, much less so against fly larvae. As 10 per cent powder, it is dusted about where insects will light upon it or crawl over it. Finely ground and diluted with flour, road dust, etc., to make a 2 per cent powder, it is used on water surfaces as a mosquito larvicide at the rate of about 0.2 lb. DDT per acre. Five per cent emulsions in water or solutions in kerosene will kill insects and larvae in similar dosage. Residual insecticidal effect persisting weeks or months is obtained when these preparations are sprayed on surfaces and screens in buildings, planes, etc., at the rate of 200 mg. per square foot of surface. The 2 per cent emulsion is used to impregnate clothes against lice. Clothes wrung moderately dry contain approximately 2 per cent by weight, the desired amount, and continue to kill lice over six to eight weeks and through as many washings.

The 4, 5, and 6 combinations are special purpose mixtures. In 4, DDT adds fly-killing powers to the original pyrethrum mosquito bomb. Spraying into the air for four seconds is enough for 1000 cu. ft. With 5, direct hits on insects are aimed at. Number 6 is made up for the special purpose of immediate killing of head, body, and crab lice. Its main use is for spraying typhus-infected patients harboring infective lice.

DDT is in no sense repellent, a fact that greatly enhances its insecticidal powers. As an insecticide, it has a slow knockdown, often delayed one to four hours or more. Mosquitoes are first activated and may escape from a treated room, but, if caught and observed for twenty-four hours, they will in many cases show a kill approximating 100 per cent. When quick knockdown is required, combinations with *pyrethrum* or *thanite*, as described, are used.

The effect of residual spraying of houses is fortunately not limited to well-constructed dwellings. Clark<sup>101</sup> reports remarkable drop in malaria infection figures in Panama by the simple measure of using residual spray DDT on ordinary, loosely put together native houses three or four times a year. He uses about twice the usual dosage and sprays inside and out. Mosquitoes are not prevented from entering and biting but die before they can become infective.

Application of DDT to natural bodies of water and outdoor areas, whether by sprayer or aeroplane, is limited by its killing effect on fish and useful insects.

DDT is almost insoluble in water, is moderately soluble in mineral and vegetable oils, and highly soluble in certain organic solvents as *cyclohexanone*.<sup>102</sup> Danger to man and animals parallels these solubility properties. Absorption is minimal and unimportant from contact with powders even when ingested in small doses, but is highly dangerous from oily solutions, whether on the skin or in the gastrointestinal tract. In ordinary careful use of dilute solutions, man is unlikely to suffer. Prolonged contact with impregnated garments has not produced local or general disturbance. Great care must, however, be exercised by workers who handle the concentrates, to protect themselves by clothing, gloves, and, at times, respirators.

Symptoms of poisoning and the amounts that produce them in man can be guessed at from animal experiments. In a single dose, it takes 150 to 3000 mg. per kilo to kill a laboratory animal<sup>103</sup> when the dose is given in oil orally, by stomach tube, by skin, subcutaneously, intramuscularly, or intraperitoneally. Smaller doses given over an extended period can also harm and eventually kill. Nervous symptoms, sensitiveness to stimuli, weakness and trem-

ors, with anorexia and rapid weight loss are the main signs. On death, no central nervous system changes are found, but there is liver damage of varying degree. If recovery occurs, liver repair is complete.

A fortunate feature of chronic DDT poisoning is the warning symptoms that appear, usually in time to forestall fatalities. If pronounced leukocytosis or nervous and muscular symptoms and weakness appear, the patient should be removed from contact with DDT at once. No antidotes to poisoning are known.

Instances of human poisoning with DDT are few but significant. An acute fatal case is reported<sup>104</sup> in a child aged one year, who died four hours after ingestion of about 1 ounce of 5 per cent DDT in crude kerosene. An adult,<sup>105</sup> who used DDT in acetone on his hands several times, at last kneading 25 gm. of it in an inert dust in acetone for some minutes, developed symptoms within a few days: heavy, aching limbs and weakness of the legs, with periods of extreme nervousness. He required bed rest ten to fourteen days, could not sleep, developed great anxiety, and on three occasions generalized muscle tremors. He was unable to work for ten weeks and not entirely recovered even after a year.

DDT has, as competitor, *gammexane* (666) ( $C_6H_6Cl_6$ ), the so-called "British DDT." It is the gamma isomer of benzene hexachloride and has properties similar to DDT. There are certain differences. *Gammexane* has good activity against house-fly larvae, as DDT has not, and it is repellent as well as insecticidal. It is, however, more toxic than DDT and gives no warning signs. If symptoms occur, death follows.<sup>103</sup>

**Repellents** — Repellents represent another chapter in protection against tropical disease. Three have been

proved especially useful, *dimethylphthallate*, *indalone*, and *Rutgers 612*. Each has some special properties of its own. *Dimethylphthallate* may be used alone, but an all-purpose repellent of the three named in 6:2:2 proportions is excellent. *Dibutylphthalate* is preferred to *dimethylphthallate* by many. Either may be applied to the skin and clothes and will remain effective some hours though sweating necessitates frequent renewal. These repellents are usefully applied to mosquito netting or even wide-meshed netting made up into gloves and veils.<sup>106</sup> A new Naval Medical Research Institute repellent, NMR1201, is recently announced. It is said to protect for nearly seven hours on the dry skin; for three hours on sweating skin.<sup>107</sup>

**Conclusion**—With all the new insecticides and repellents, emphasis has heretofore been concentrated on military usefulness. Now at length their limitations and uses for civilian purposes will gradually become more clearly defined. They will be a boon to us all but may well prove particularly valuable among indigenous peoples where facilities and funds for more cumbersome and expensive methods of disease control have been largely lacking.

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## NEUROLOGY

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### Encephalitis

During the last two decades the study of viruses has assumed great importance. The diagnosis of virus diseases is confused by frequent association with infectious processes having similar clinical manifestations. Laboratory studies now indicate that serologic procedures (neutralization and complement-fixation tests) are applicable even in the absence of virus recovery. Hammond,<sup>1</sup> in a review of the encephalitides of virus origin, presents the following table:

Hammond emphasizes the fact that the virus group of encephalitides, as a whole, presents greater difficulties of diagnosis and is sufficiently complicated to warrant separate consideration. He separates this group from the protozoal, spirochetal, bacterial, fungus, rickettsial, and chemical or toxic types of encephalitis.

He and his co-workers<sup>2</sup> review their findings in the study of the epidemics of encephalitis that have occurred in the Yakima Valley, Washington. Their present report is concerned with the last of these outbreaks. Titration of antibodies in acute and convalescent phase serums established a diagnosis of western equine or St. Louis encephalitis in eleven patients. The fatality rate was 7.2 per cent. Forty-nine strains of virus were isolated from four species of mosquitoes and activity of the *Culex tarsalis* mosquito correlated with the epidemic wave. Maternal transmission of the St. Louis antibody to two infants occurred in their series of cases. Antibody studies in that season's chickens indicated that 30 to 50 per cent had been infected with Western

equine virus but very few with the St. Louis virus. This correlated well with the proportion of the two viruses isolated from the mosquitoes.

Sulkin<sup>3</sup> collected chicken mites, fowl ticks, and serum from barnyard fowl on nine ranches and farms in Dallas County, the center of the 1944 epidemic of equine encephalomyelitis. The mites and ticks were kept in test tubes without feeding and then used for inoculating either mice or guinea pigs. All of the guinea pigs and half of the mice thus inoculated showed typical symptoms of encephalitis by the fourth or fifth day. Filtration experiments and neutralization tests showed the infectious agent thus transmitted to be a typical western strain of encephalomyelitis virus. Sulkin has demonstrated that chicken mites form a permanent deposit for equine encephalomyelitis virus in Dallas, from which hens may be directly infected, and man and horses infected indirectly by other insect vectors (mosquitoes).

Randall<sup>4</sup> maintains that equine encephalomyelitis is the most important horse disease in the United States at the present time. The knowledge that the three types of equine encephalomyelitis enzootic in the Western Hemisphere (eastern, western, Venezuelan) are pathogenic for human beings and the relatively high mortality rate of the human disease emphasizes their importance from the public health standpoint. The evidence is ample that the disease is transmitted through insects, particularly mosquitoes. Horses and mules may be protected against the disease by the

TABLE I  
ENCEPHALITIS OF KNOWN VIRUS ETIOLOGY

<i>Epidemic Type, Usually Seasonal</i>		<i>Sporadic Type</i>	
<i>Name</i>	<i>Mode of Transmission</i>	<i>Name</i>	<i>Mode of Transmission</i>
1. Poliomyelitis.....	{ Probable contact Infection	1. Mumps.....	{ Contact
2. Japanese "B".....		2. Lymphogranuloma venereum.....	
3. St. Louis.....	{ Arthropod-borne	3. Rabies.....	{ Bite
4. Western equine.....		4. Virus B.....	
5. Venezuelan equine....		5. Lymphocytic choriomeningitis	{ Unknown
6. Russian Spring- summer.....		6. Pseudo chorio- meningitis.....	
7. Eastern equine.....	{ Probably Arthropod-borne	7. Herpes simplex....	
8. West Nile.....		8. Measles ?.....	
9. Semliki Forest.....		9. Influenza ?.....	
10. Australian X.....	{ Unknown		
11. Focal hemorrhagic meningoencephalitis			

ENCEPHALITIDES OF QUESTIONABLE VIRUS ETIOLOGY

<i>Epidemic Type</i>		<i>Sporadic Type</i>	
<i>Name</i>	<i>Mode of Transmission</i>	<i>Name</i>	<i>Mode of Transmission</i>
1. Von Economo Type	Unknown	1. Post Infection.....	{ Unknown
		2. Post Vaccinal.....	

annual administration of chick tissue vaccines.

**Treatment** — Nicholson<sup>5</sup> reports a case of lethargic encephalitis and a case of polioencephalitis, in both of which pooled adult plasma was given with favorable results. He suggests that this method of treatment might be used in epidemics of poliomyelitis because the cases presented were of a severe encephalitic type and gave the use of blood plasma a severe test.

Portmann and Lough<sup>6</sup> report their results in forty-nine patients suffering from acute encephalitis who were treated with *roentgen therapy*. They feel their results were sufficiently encouraging to

merit the use of roentgen therapy as a method of treatment. The best results were obtained when roentgen therapy was given before degenerative changes were established in the central nervous system. No patient with a chronic form of encephalitis or with a postencephalitic syndrome was benefited by the irradiation. All patients were treated as others with inflammatory processes might be treated, and the technical factors were essentially the same in each case. The average skin dose was 75 to 100 r to each side of the head including the base of the skull, given daily or on alternate days usually for a total of 300 r, or less. The spine was treated in a few cases

with evidence of encephalomyelitis. In their series of forty-nine cases, 59.1 per cent were considered recovered and 30.6 per cent improved.

### Encephalomyelitis

Mackay<sup>7</sup> reports three cases of what he terms acute encephalomyeloradiculoneuritis. The cases are really a variety of a syndrome which has been described as the Guillain-Barre syndrome. He indicates that the name he employs to describe his cases is unwieldy. He points out the most important feature of the syndrome is the so-called albuminocytologic dissociation. Other terms which have been used to describe similar cases or closely allied entities are: Acute infectious neuronitis; acute infectious polyneuritis; polyradiculoneuritis, and myeloradiculoneuritis. He points out that the disease is an acute pleomorphic involvement of the central nervous system usually following upper respiratory infection and characterized by parasthesias and pains, widespread neuronal motor weakness of the extremities, and frequent involvement of the seventh or other cranial nerves. Sometimes the cerebrospinal axis is involved. This clinical picture is often associated with the elevation of the total protein content of the cerebrospinal fluid without significant increase of the cell count. Although a virus is suspected as the causative agent, it has not been isolated. Treatment must be only symptomatic until more is known of the cause of the disease. Respiratory paralysis may require the use of a *respirator*. *Physiotherapy* may be very useful in the acute stage in the prevention of contractures and restoration of maximal muscular function.

Marsh and DeVine<sup>8</sup> describe four cases of neuromyelitis optica which were associated with albuminocytologic dis-

sociation. One of these patients, in addition to the above, developed symptoms of widespread involvement of the peripheral and central nervous systems. At necropsy, a typical disseminated myelitis was demonstrated. A combination of clinical symptoms and cerebrospinal fluid changes typical of neuromyelitis optica, Guillain-Barre syndrome, and disseminated encephalomyelitis found in the same individual at different steps of the illness suggests that this group of diseases which has been frequently classified as separate entities may, under some circumstances, be caused by the same etiological agent.

### Electroencephalography

During the past few years, electroencephalography has been applied more generally and in a greater variety of combinations than ever before.

Hursh<sup>9</sup> presents evidence that the origin of petit mal seizures may be subcortical. It is interesting that, despite the current emphasis which has been placed on the electroencephalogram detection of the epileptogenic focus for a certain group of patients displaying generalized convulsions, no such demonstrable cortical lesions have been shown to constitute the focus for attacks of petit mal epilepsy. The hypothesis that the focus for petit mal epilepsy may be identified by the usual electroencephalographic technics receives support from the work of Penfield and Erickson. These authors reported a case of petit mal epilepsy for which the focus was identified by implanting electrodes in the region of the interpeduncular space. Hursh found that the postoperative records of two patients with nearly complete section of the corpus callosum showed "petit mal" sequences displaying a simultaneous onset in bilaterally symmetric leads. Since conduction between



the two hemispheres *via* axon paths in the corpus callosum had been destroyed, the existence of a cortical focus could not be assumed in these particular patients. Hursh considers the thalamus or the hypothalamus as a tentative site for the pacemaker of the spike and wave complex which is characteristic of the petit mal record.

Cohn<sup>10</sup> studied the electroencephalogram records in patients who had had prefrontal lobotomy. He found that the primary electroencephalic response of the human brain to localized injury (prefrontal lobotomy) was the production of persistent or transitory focal slow waves. With lobotomized patients, the return of the electroencephalographic pattern to a relatively normal state usually required one to three months. Some patients showed no demonstrable response to cerebral injury. A representative group of subjects showed apparent normal early recovery and then again exhibited grossly abnormal variations in potential in the region of the original injury. At times the abnormality was general. The author concludes that the aforementioned phenomena are general and thus apply to injury to the brain from other traumatic agents.

Bagchi and his colleagues<sup>11</sup> report on their study of the electroencephalogram and clinical effects of electrically induced convulsions in the treatment of mental disorders. In a series of fifty-four patients suffering from different types of mental disorders, they found that 50 per cent of the cases had normal and 50 per cent borderline abnormal preshock electroencephalograms. A definite similarity between the epileptic and shocked brain was noted. There was a statistical indication that patients having psychoneurosis with obsessive compulsive and depressive features and the highest preshock abnormal and borderline electro-

encephalograms profit by such treatment more as a group than schizophrenics with or without depression. There was a suggestion that patients with preshock borderline abnormal electroencephalograms profit more as a group by shock treatment than those with normal electroencephalograms.

Greenblatt and Levin<sup>12</sup> studied the electroencephalogram in neurosyphilis. They found that 50 per cent of 233 of these cases had abnormal electroencephalograms. In a control group, the incidence of abnormality was 10 per cent. The incidence of abnormality in the various clinical types of neurosyphilis was as follows: Meningovascular lues, 60 per cent; general paresis, 55 per cent; tabes, 14 per cent; optic nerve atrophy, 44 per cent. Why optic nerve atrophy cases should have a high incidence of abnormal electroencephalograms is a mystery to the writers, as it was to Finley and his co-workers who had similar findings in 1942. It is to be noted that tabes did not have a significantly greater incidence of abnormal electroencephalograms than controls. Twenty per cent of the total cases with neurosyphilis had positive histories of seizures as compared to an incidence less than 1 per cent in the general population. A very high incidence of abnormal electroencephalograms (90 per cent) occurred in the cases with a history of seizures. The more abnormal the electroencephalogram in any given case of neurosyphilis, the greater the likelihood that the patient had a history of seizures. No correlation was obtained between the electroencephalographic abnormality and abnormal pupils, or between electroencephalographic abnormality and presence of delusions or hallucinations as a primary part of the mental picture.

In the past few years, the electroencephalographic recordings have been

used to obtain direct information as to disturbances of cerebral function resulting from hypoglycemia. Strauss and Wechsler<sup>13</sup> point out that electroencephalography may be used to help establish the presence of a borderline blood sugar value in lesser hypoglycemic states whose symptomatology is uncharacteristic. The latter may consist of fatigue, headache, dizziness, irritability, restlessness, and a host of minor neuropsychiatric manifestations, many of which are grouped under the psychoneuroses. They report two cases of spontaneous hypoglycemia which were associated with abnormal electroencephalograms. The relationship between the presence of nervous complaints in the early morning and the development of delta activity on hyperventilation in the fasting state was studied. Delta activity developed more frequently in subjects having such complaints than in subjects without them.

Brazier and Finesinger<sup>14</sup> studied the electroencephalographic recordings in patients who had received barbiturates intravenously. In every subject to whom the barbiturate was given, the electroencephalogram showed the development of high voltage activity. In every subject the high voltage fast activity appeared first in the frontal leads, then in the parietal leads, and finally in the occipital leads, and it disappeared in the reverse order. In other words, the regions of the cortex which are the most recent in the phylogenetic development were most vulnerable to the action of the barbiturates, as evidenced by the electroencephalogram.

Greenblatt and his collaborators<sup>15</sup> report the conclusions of their study of the electroencephalograms of patients with bromide intoxication. They found that the incidence of electroencephalographic abnormality was high during the intoxicated state and a progressive clear-

ing of the patient's sensorium paralleled electroencephalographic changes toward normal. At high blood bromide levels (over 200 mg. per 100 cc.) the electroencephalogram tended to show diffuse slow activity, and the patient as a rule was confused and dysarthric. As the bromide level fell, the electroencephalograms of a number of patients showed a phase of mixed slow and fast activity, and at low levels of bromide concentrations the electroencephalograms showed essentially normal or mildly fast rhythms. The authors emphasize the fact that there are striking individual differences in the electroencephalogram and clinical picture at the same blood bromide level. Kennard and her co-workers<sup>16</sup> studied the electroencephalographic changes in delirium tremens. The electroencephalograms of forty-seven patients with this condition showed definite characteristics which contrasted with a normal control group and with those of twelve alcoholics without delirium tremens. They showed a relatively high incidence of fast 16 to 30 per second low voltage activity, the incidence of which decreased with the recovery of the patient. Those who showed the greatest fast activity and lowest amplitude at the onset were the slowest to recover. They were also the least stable socially in the intervals between their alcoholic episodes. Records of the twelve control alcoholics, either in the acute stage of alcoholic intoxication, markedly deteriorated, or with polyneuropathy, did not show the increased fast activity and low alpha index seen in patients with delirium tremens. The authors conclude that the electroencephalographic characteristics of delirium tremens are directly concerned with that syndrome or with some phase of it. Gottlieb and his associates<sup>17</sup> report a high incidence of abnormality in the

electroencephalograms of children with primary behavior disorders. In a series of sixty-seven children, none of whom presented signs of organic brain disease, or in whose condition an organic etiologic factor was suspected, 49 per cent had abnormal electroencephalograms. Significantly, greater proportions of abnormal electroencephalograms were found when there was either a history of psychosis, maladjusted personality, chronic alcoholism, or epilepsy in the family or a personal history of cerebral trauma or severe illness than when none of these factors was present.

### Epilepsy

The Public Affairs Committee of New York,<sup>18</sup> with the aid of a number of leaders in the field of epilepsy, has made available a useful realistic consideration of the disease. Causes and diagnostic methods of the illness are discussed, including a simple, clear explanation of the electroencephalogram. Modern methods of treatment are outlined. Sensible advice about sending children with seizures to school and about marriage and parenthood is given. An encouraging survey of industrial opportunities for the epileptic is outlined. Doctors dealing with epileptic patients and their families might find it advantageous to give a copy of this pamphlet as a planned part of the therapeutic regimen. Moore<sup>19</sup> reviews the aberrant forms of epilepsy and emphasizes that they may be disguised in numerous somatosensory, psychic, and unusual motor displays. There are numerous manifestations of aberrant forms of epilepsy, such as vertigo, paroxysmal transient headaches, fleeting sensory disturbances consisting of numbness, tingling, pain, sense of heat or cold, sense of swelling, and sense of movement; nausea, vomiting, choking sensations, visual sensations as scoto-

mata, micropsia, and macropsia; ocular pain, olfactory and auditory disturbances; abdominal pain, disorders of gastrointestinal motility; vasomotor phenomena, dreamy states, temper tantrums, hallucinatory episodes, various automatisms, short explosive motor acts, and others which may readily be attributed to some local visceral physiologic disturbance or organic disease, or because of insufficient supportive data may be dismissed as harmless transient symptoms, but which, upon investigation, in many cases, are found to be abortive epileptic aura or types of epileptic variants.

Weinberg<sup>20</sup> describes a special group of five cases in which the convulsive seizures appeared only after excessive fatigue; their management did not require the usual treatment of epilepsy. The term "latent epilepsy" is considered as the most likely to describe this type of case. The convulsions appeared in these cases only after a more or less prolonged and intensive period of activity. None of the patients required epileptic therapy. Abstinence from excessive fatigue was the only prerequisite to prevent seizures. The author failed to establish hypoglycemia as a cause of the seizures. Himler and Raphael<sup>21</sup> report on their followup study on ninety-three college studies with epilepsy. From their study it is evident that the presence of seizures in individuals with higher intelligence does not necessarily constitute a barrier to academic training on the college level or to successful personal, social, and vocational adjustment after leaving college. It is noteworthy that forty-four (47.3 per cent) of the group graduated from college. Among these were three with medical degrees, six with law degrees, and eight with master's degrees. If those still continuing in their studies and those who could continue were added to those who grad-

uated, the total number who were capable of creditable work in the university would reach sixty-five, or 69.9 per cent. A study of the vocational and occupational adjustments made by sixty-three concerning whom this information was available at the time of the study gave very interesting results. Of these, fifty-four have made entirely satisfactory personal adjustments, three have chronic neurotic reactions, four show basic personality instability, and only two are known to have deteriorated, one with paranoid elaboration.

Lennox and Collins<sup>22</sup> report on their investigations of the intelligence of normal and epileptic twins based on ninety-three twins of various ages. Of these, sixty-three twins were without a history of epilepsy or brain injury and thirty had a history of seizures. Their data suggest that with a good mental inheritance, a patient is able to maintain a normal intelligence despite epilepsy, but that gross acquired pathology of the brain has a serious effect on mentality. In other words, a person with a normal mentality who develops idiopathic epilepsy is much less likely to become mentally deteriorated than a person who develops symptomatic epilepsy. Loscalzo<sup>23</sup> presents a preliminary report on the treatment of epileptic patients with a combination of 3-methyl 5, 5 phenylethyl-hydantoin and phenobarbital. The drug he used is a new hydantoin derivative. This new derivative combined with phenobarbital is known as *hydantal*. Each tablet of hydantal contains 0.2 gm. ( $\frac{1}{3}$  grain) of phenobarbital and 0.1 gm. (1.5 grain) of 3-methyl 5, 5 phenylethyl-hydantoin. He treated seventeen patients suffering from epilepsy of organic and unknown etiology with hydantal. In most cases, petit mal attacks were associated with grand mal attacks. He prescribed 1 to 6 tablets of hydantal daily, the average

being 3. Treatment was continued in this series for an average period of sixteen months. Grand mal seizures were reduced approximately 60 per cent and improved emotional status was noted consistently. Petit mal attacks continued in the same ratio as with *dilantin sodium*. The incidence of side effects as compared with sodium dilantin was strikingly low. Gum hyperplasia occurred in two cases. Caplan<sup>24</sup> examined the possibility of replacing epileptic fits which may occur at any time by convulsions electrically induced under controlled conditions of time and place. He emphasizes the fact that this therapy should not supersede the pharmacologic methods of combating fits but urges it as an accessory treatment in those cases in which fits occur despite full dosage of anti-convulsant drugs. Fifteen male epileptics were treated for periods of three to nine months. All but one were inpatients of a public mental hospital. All had psychoses associated with epilepsy. Convulsions were electrically induced once or twice a week, depending upon the reactions of the individual patient. In eleven patients, the fits were markedly diminished. In seven patients, the symptoms of an associated psychosis were ameliorated. One patient with frequent furors had cessation of his attacks after the convulsion treatment. Another patient who suffered from psychic equivalent in the form of periods of aggressiveness and bad temper uncontrolled by drugs was helped remarkably with electrocerebral treatment. No serious or alarming complications resulted from this treatment. Lennox<sup>25</sup> reviews the subject of epilepsy. He emphasizes the fact that the causes of seizures are multiple and that treatment must be individual and many-sided. Diet, dehydration, activity, and drugs are four practical methods of increasing the patient's re-

sistance to seizures. Patients should eat what other members of the family eat, if their diet is sensible and balanced. Dehydration in a number of cases increases a patient's resistance against seizures. In order to produce a net loss of tissue fluids, the total fluid intake must be reduced to 20 ounces or less a day, not counting the water content of solid food. The check on effectiveness is a decrease in body weight with the total calorie intake remaining the same. Patients experience chronic thirst so that, in spite of its simplicity, the procedure is not popular. Dehydration should be continued only as trial demonstrates an actual reduction in the number or severity of seizures. Patients with frequent severe seizures or with definite underlying cerebral pathology are least likely to be helped. Activity is desirable. Physical work and exercise are required for good health. The acidosis induced by activity of brain and muscle cells lowers the seizure threshold, and mental activity tends to reduce abnormalities of the brain wave pattern; seizures are most frequent during sleep or during times of physical and mental relaxation. The anticonvulsant drugs to be used in the order of their effectiveness in controlling seizures are *dilantin sodium*, *phenobarbital*, and *bromides*. *Dilantin sodium* is most effective for the psychomotor type of seizure and is relatively noneffective for petit mal. The effective dose may approximate the dose at which side effects appear. Therefore the physician beginning with 0.1 gm. (1½ grains) three times a day for adults and half that amount for children should gradually increase the amount until seizures are controlled or toxic symptoms appear. A good many patients who are not controlled by this drug alone are benefited by the addition of phenobarbital. *Phenobarbital* can be given in daily doses for

adults from 0.1 to 0.3 gm. (1½ to 3 grains), although double this amount may be taken. In moderate doses it may be taken for many years without apparent deleterious effect or the formation of a habit. Six-tenths to 1.2 gm. (10 to 20 grains) of *sodium* or *potassium bromides* may be given three times a day, usually in a watery solution. For accurate treatment, the bromide content of the blood should be measured at periodic intervals. *Mebaral* is a barbiturate which occasionally is more effective than phenobarbital, especially in patients with petit mal. It is given in 0.2-gm. (3-grain) tablets from one to three times a day, the limiting factor usually being drowsiness. In the presence of status epilepticus, soluble phenobarbital sodium may be given parenterally in 0.2- to 0.5-gm. (3- to 5-grain) doses, repeated every twelve hours if necessary. When other means fail and exhausting convulsions threaten life, *etherization* may be resorted to.

Lennox<sup>25a</sup> reports his results in the treatment of petit mal (pyknolepsy) with a new drug, *tridione*, 3, 5, 5-trimethyloxazaldidine-2, 4-dione. He states it is the most dramatic in its effect of any form of therapy attempted in the treatment of this form of epilepsy. Fifty patients, each having many daily seizures either myoclonic or akinetic, were treated with tridione for from two to fifteen months. All but four of the patients were less than twenty years of age. The duration of the illness was from one to eighteen years. Practically all of the group had been given the usual anticonvulsant drugs without important benefit. In no case was the transfer to tridione accompanied by an increase of petit mal. Of this group of forty patients, eleven (28 per cent) now are free from petit mal and twenty-one (52 per cent) have experienced a 75 per cent

or greater reduction in the number of seizures from the previous level. Ten (20 per cent) were helped only moderately. None failed to experience some amelioration of seizures. Therapy was discontinued in two cases because of toxic symptoms. A group of ten patients, in addition to frequent petit mal seizures, experienced frequent grand mal seizures. Results with this group were encouraging as regards disposal of petit mal but disappointing as regards grand mal. The dose of tridione which proved effective against petit mal was without influence against grand mal. The medicine is dispensed in capsules each containing 0.32 gm. (5 grains). Doses used varied from 1.0 to 2.0 gm. (15 to 30 grains) a day without much regard for age.

**Narcolepsy** — Narcolepsy is a syndrome characterized by diurnal somnolence and catalepsy. The latter term refers to a loss of muscle tonus, involving sometimes a small group of muscles and sometimes all the muscles of the body, and causing spontaneous attacks of powerlessness. Harper<sup>26</sup> reports four cases in whom these symptoms were entirely relieved by *amphetamine sulfate*. The dosage varied from 10 to 30 mg. of amphetamine sulfate daily. There was no evidence of addiction or habit formation in these patients although some tolerance to the drug was developed.

### Intracranial Vascular Disorders

**Subarachnoid Hemorrhage** — Wolff and his collaborators<sup>27</sup> investigated the prognosis of subarachnoid hemorrhage in forty-six patients with the disorder. Subarachnoid hemorrhage is responsible for 2 per cent of all sudden deaths. Twenty-nine per cent of the patients with subarachnoid hemorrhage died during the first episode of bleeding, 14 per cent died during recurrent bleeding between the second and fourth weeks after the initial

hemorrhage, and an additional 5 per cent died by the end of the first year. The majority of the remaining patients who survived the first year were alive three or four years after the initial hemorrhage. Some die in from one to twenty-seven years of a recurrence of the subarachnoid hemorrhage. A few may live twenty-seven years or longer after the first attack without recurrence. The authors recommend that patients who come under observation during the first four weeks after the subarachnoid hemorrhage be subjected to arteriography and subsequent craniotomy if an aneurysm is visualized. Those who have had their last hemorrhage more than four weeks previously and who have localizing signs of an intracranial mass should have arteriography and subsequent craniotomy if suitable indications exist. When the localizing signs are absent in these patients, arteriography and appropriate air studies may be performed.

Alpers and Forster<sup>28</sup> studied the reparative processes in subarachnoid hemorrhage. In their series of cases, the process of organization in no instance extended into the cortex. No evidence of adhesions of the pia or of extension of the connective tissue changes along the parenchymal blood vessels could be discovered. From this it would seem that at least within the time limits of survival in their reported cases (survival periods ranging from a few hours to thirty-five days), the parenchyma of the central nervous system was not impaired by the process of organization occurring in the subarachnoid space.

Taylor and Page<sup>29</sup> discuss the signs and symptoms of impending cerebral hemorrhage in cases of arterial hypertension. Records of forty patients who died with essential hypertension were examined to determine whether or not the clinical course of those who died

from cerebral hemorrhage were similar enough to allow an accurate prediction of apoplexy. Among this group, nineteen had fatal cerebral hemorrhage. Five signs and symptoms were consistently observed. These were (1) severe occipital or nuchal headache, (2) vertigo or syncope, (3) motor or sensory neurological disturbances, (4) nose bleeds, and (5) retinal hemorrhages in the absence of papilledema or exudate. These findings were negligible or absent among those patients who died from other causes. It is concluded that demonstration of any four of these manifestations in persons with essential hypertension warrants the assumption that death from cerebral hemorrhage will occur within nine and one-half months to five years (average 2.1 years).

### Meningitis

The utilization of the antibacterial agent, *penicillin*, in the treatment of bacterial meningitides continues to be the most important development in chemotherapy.

Thus far it has proven to be nontoxic in man in maximum therapeutic doses. It is highly effective against a wide variety of micro-organisms of the gram-positive group. It is effective in the treatment of syphilis. There are two salts of penicillin available for clinical use—sodium and calcium salts. They are equally effective therapeutically and they can be used interchangeably. The commonest route of administration is intramuscular, and it is the route of choice. Injections may be given intermittently or continuously. It may also be given intravenously and into the subarachnoid space.

Keefer<sup>30</sup> states it is difficult to make any absolute rules concerning the necessary dosage of penicillin that will be universally applicable. One of the greatest

difficulties in assessing dosage is the lack of signs of toxicity, so that the maximum tolerance dose is not known. He feels that in all cases with bacteremia the treatment should be continued for two to three weeks and enough penicillin given to bring the infection under control. He and his co-workers<sup>31</sup> discuss thoroughly the dosage of penicillin in the meningitides. They offer the following outline of treatment in serious infections with or without bacteremia: They feel that an initial dose of 15,000 to 20,000 Oxford units should be given with continuing dosage as follows: (1) Constant intravenous injection of isotonic solution of sodium chloride containing penicillin so that 5,000 to 10,000 Oxford units are delivered every hour, making a total of 120,000 to 240,000 Oxford units in a twenty-four-hour period; one half the total dose may be dissolved in a liter of isotonic solution of sodium chloride and allowed to drip at the rate of 30 or 40 drops per minute. (2) If a continuous intravenous drip is undesirable, 20,000 to 40,000 units may be injected intramuscularly every three or four hours. (3) After the temperature has returned to normal, the penicillin may be continued as long as there are any signs of active infection. (4) Penicillin does not penetrate the subarachnoid space in appreciable amounts, so that it is necessary to inject penicillin into the subarachnoid space or intracisternally in order to produce the desired effect. Ten thousand units diluted in isotonic solution of sodium chloride in a concentration of 10,000 units per cc. should be injected once or twice daily, depending upon the clinical course and the presence of organisms.

Shalom,<sup>32</sup> on the basis of his observations in a series of eleven cases of purulent meningitis, believes there is often a partial and sometimes a complete obstruc-

tion to the flow of the cerebrospinal fluid at the foramen magnum, produced by the raised intracranial tension. He feels this obstruction impedes the dosage of penicillin to the cerebral circulation where it is needed most when the drug is given intrathecally. He believes that obstruction to the cerebrospinal fluid at the foramen magnum can be reduced or overcome by the intramuscular administration of hypertonic dextrose solution. This solution, by reducing intracranial tension, tends to prevent or minimize the formation of hydrocephalus and its sequelae. Penicillin is dissolved in this solution and the two injected together every three hours. He found that these solutions facilitated the intrathecal flow of penicillin to the cerebrospinal fluid and also prevented or minimized other undesirable effects produced by the raised intracranial tension. He used a 20 per cent dextrose solution in physiological sodium chloride.

**Meningococcic Meningitis**—Keefer<sup>30</sup> states that *sulfadiazine* continues to be the drug of choice in the treatment of meningococcic meningitis. While *penicillin* is effective in controlling this disease, the response is slower than following the use of sulfonamides, and it continues to be necessary to give penicillin both systemically and intrathecally. In cases which prove resistant to the sulfonamides after a period of twenty-four to forty-eight hours, penicillin should be started at once. Penicillin is the drug of choice in the treatment of infections of the meninges due to pneumococcus, staphylococcus, and hemolytic streptococcus. Treatment, he emphasizes, should be started as soon as the diagnosis is established, and all foci of infection in the neighborhood which can be drained surgically should be taken care of at the same time. This is especially true when there is an asso-

ciated mastoiditis or lateral sinus thrombosis.

Reinhold and his associates<sup>33</sup> report the response of patients suffering from meningococcic meningitis to treatment with *sulfamerazine* with particular reference to the concentration of this substance in body fluids. Their results indicate that the dosage in common use is suboptimal and that further trials with therapeutic concentrations in the blood serum above 20 mg. per 100 cc. are needed. Harford and his associates<sup>34</sup> report a case of fulminating meningococcic meningitis which responded dramatically to penicillin after forty-eight hours of treatment with sulfamerazine which had failed to influence the infection.

Meyer<sup>35</sup> reports on the result of treatment in 165 cases of meningococcic meningitis. Sulfadiazine was the main therapeutic weapon but meningococcus *antitoxin* and repeated lumbar punctures to relieve increased intracranial pressure were valuable adjuncts in certain instances. Of 150 cases proven bacterially, the mortality rate was 4 per cent. In adults, 5 gm. of sodium sulfadiazine in 1 liter of physiological saline were administered intravenously and, in most instances, this was followed by 1 gm. orally every four hours. It was only occasionally necessary to give subsequent doses of sulfadiazine parenterally, as the Levine tube proved to be an effective instrument for the administration of medication and fluids during coma. A fluid intake of at least 3 liters a day was maintained and sodium bicarbonate was given to promote alkalization of the urine. In children, an initial dose of 0.1 gm. per kg. of sodium sulfadiazine was administered parenterally followed by oral doses calculated on the basis of 0.2 gm. per kg. In all instances, an effort was made to maintain a sulfadiazine blood level of approximately 10 mg. per



100 cc. Sulfadiazine could be usually discontinued on the ninth day of treatment. Those patients who failed to respond to sulfadiazine in twenty-four hours or who on entry gave evidence of overwhelming infection, were given meningococcus antitoxin. In the age group below ten years, the average total dosage of antitoxin was 20,000 units, the largest dose being 80,000 units. In the age group above ten years, the average total dose was 50,000 units, the largest being 120,000 units. The antitoxin was given in a single dose, one half intravenously and the remainder intramuscularly.

Winter<sup>36</sup> gives his results in the treatment of meningococcic meningitis in children with a single large intravenous dose of sodium sulfadiazine. Eight patients received 2.5 gm. per pound of body weight and one patient received 2 gm. per pound. This single dose resulted in complete recovery. He found the dose would maintain a sulfonamide level in the spinal fluid and blood long enough for rapid recovery. Spinal fluid cultures were sterile twenty-four hours after a single large intravenous dose of sulfadiazine, lessening the chance for complications and sequelae.

White and his associates<sup>37</sup> report the occurrence of six deaths in a series of twelve cases. They emphasize these results serve to illustrate the limitation of penicillin in controlling the more severe and resistant meningococcal infections. Seven of the twelve patients were given penicillin after adequate sulfonamides were given. In two of the seven, there was no bacterial evidence of infection when penicillin was started. Four of the seven patients died. Penicillin and sulfonamide were combined in two patients, both of whom recovered. Only five of the twelve patients were given intrathecal therapy; three of the five died.

The systemic dose used was 100,000 units daily except for two children, both of whom received 50,000 units each day. Among those to recover, the average total dose was 750,000 units during an average of 6.5 days of treatment.

Applebaum<sup>38</sup> considers sulfadiazine as the drug of choice in the treatment of purulent meningitis. He recommends the following plan of dosage: On the first day of treatment, children under one year of age receive from 2 to 5 gm.; children from one to three years of age receive from 3 to 5 gm.; children above that age receive from 4 to 7 gm., and adults from 9 to 12 gm. One fourth to one third of this amount is given as the initial dose and the remainder divided and administered at intervals of four hours. The drug may be given orally, intravenously, or subcutaneously. It is his belief that parenteral routes should be reserved for severe cases and for those patients who are unable to take or unable to retain the oral administration. He does not recommend the use of the drug intrathecally. He feels it is undesirable to give large amounts of the drug simultaneously by vein and by mouth. It is essential that during the course of the sulfonamide therapy the patient receive a sufficient amount of fluid to maintain an adequate renal output. He recommends the administration of at least 3000 cc. of fluid a day in order to assure an output of 1200 cc. or more daily. He has obtained prompt and consistent results in treatment with drug levels in the blood and cerebrospinal fluid ranging from 10 to 15 mg. per 100 cc. in the blood and from 7 to 10 mg. per 100 cc. in the cerebrospinal fluid. He has found penicillin less satisfactory than the sulfonamides but recommends penicillin as an adjunct to sulfonamides in the treatment of the fulminating form of the disease. It is also of value in the

treatment of patients who are hypersensitive to sulfonamides or who have developed a sulfonamide intoxication.

Ballard and Millar<sup>39</sup> review the sequelae of cerebrospinal meningitis in sixty cases. Fifty-three patients showed symptoms, these being severe in twenty-three, moderately severe in twenty-three, and very mild in seven. Most of the cases were seen three to six months after the acute illness. In thirty-four of the fifty-three symptomatic cases, the outstanding complaint was headache; in seven, lassitude; in three, backache, and in three, "effort" symptoms. The symptoms listed in order of frequency of occurrence were headache, failure of concentration, backache, insomnia, depression, postural dizziness, functional ocular symptoms, muscular limb pains, effort symptoms, poor memory, dyspepsia, and vertigo. Full neurological examination revealed organic signs in only seven cases. One had an external rectus palsy, two had diplopia lasting for some weeks but finally clearing up, one a facial palsy, one case had transient weakness of ocular convergence, and one had persistent unilateral tinnitus with slight nerve deafness. The authors felt that the determining factors in the severity and persistence of the subjective residual symptoms following cerebrospinal meningitis was in ratio to the severity of the acute illness and, more strikingly, the degree of psychoneurotic predisposition as determined by personality study. Of forty-nine cases treated by superficial psychotherapy and graduated exercises, forty-five were returned to duty and four invalided. None of these forty-nine cases had any organic neurological findings. The writers suggest that the symptom complex following cerebrospinal meningitis should be regarded as a psychosomatic reaction. Suggestion, whether by doctors or others, played a significant

part in the production and perpetuation of symptoms.

Corfield<sup>40</sup> reports the case of a patient who had five separate attacks of meningococcic meningitis. The intervals between the attacks were two years, fourteen months, one year, and eight months. He emphasizes that the recurrence of meningococcic meningitis after short periods has been recorded, but there are very few published examples of true second attacks.

**Pneumococcic Meningitis**—Keefer<sup>30</sup> points out that before the use of the sulfonamides, pneumococcic meningitis was invariably fatal. Between 40 and 50 per cent of patients recover following the use of either *sulfonamide* or *penicillin*. He states there is evidence that the combination of *sulfadiazine* and penicillin may be better than either drug alone. One of the reasons why pneumococcic meningitis is such a serious disease is that it is frequently a metastatic lesion following pneumococcus lobar pneumonia with or without an associated bacterial endocarditis. It may be a complication of craniocerebral injuries, otitis media, mastoiditis, or suppurative sinusitis of the ethmoid or sphenoid cells. Another reason for the severity of this infection is that it tends to produce hydrocephalus and encephalitis which may lead to cerebral atrophy and profound neuropsychiatric disturbances.

Harford and his colleagues<sup>34</sup> treated nine patients having pneumococcic meningitis with penicillin. All but one recovered. Mastoidectomy was performed in five of the nine cases. The importance of continuing treatment for some time after the signs of meningitis have subsided was emphasized by the occurrence of relapses in three patients. Each of the three suffering from relapses responded to therapy and eventually recovered.

Lumbar punctures were performed on all patients within twenty-four hours of the initial intrathecal injection of penicillin and in every instance the cerebrospinal fluid had become sterile. From this group of cases they felt that any demonstrable foci of infection should be drained surgically and that penicillin treatment should be continued for at least one week or more after clinical manifestations of meningitis had subsided. The usual initial intrathecal dose employed in the treatment of meningitis was 20,000 units in 2 cc. of isotonic solution of sodium chloride. Further intrathecal injections were given each day in decreasing amounts and were continued until all signs of meningitis had subsided.

White and his co-workers<sup>37</sup> treated fifty cases of pneumococcic meningitis with penicillin. The mortality in this series was 64 per cent. They conclude that, in comparison with more recent reports on sulfonamide therapy, this does not suggest that any very significant advance has been made in the treatment of this condition with penicillin. In twenty-nine cases, the meningitis occurred secondary to uncontrolled infection in the air sinuses of the head. In twenty-three instances, the primary focus was found in the middle ear or mastoid. On several occasions it was noted that patients improved primarily with penicillin therapy, then entered a prolonged period of low grade sustained infection or repeated infection. Among the patients who recovered, the average total dose of penicillin was 1,400,000 Oxford units, and the average duration was 15.5 days. All but seven of the fifty cases received intrathecal therapy. Two infants, one four weeks of age and another four months old, received intraventricular penicillin through the anterior fontanel. The older patient recovered and the other died within forty-eight hours with-

out evidence of trauma or reaction to the procedure. Intracisternal penicillin therapy was given to fifteen patients without ill effect, except in two cases in which fluid was slightly bloody at the next tap. Both of these patients recovered from the meningitis. Four patients who had failed to improve from the intraspinal therapy responded promptly to intracisternal therapy; all four recovered.

Applebaum and Nelson<sup>41</sup> report their results with penicillin in the treatment of sixty-seven consecutive cases of pneumococcic meningitis. The penicillin in these cases was administered intrathecally, intravenously, or intramuscularly. The majority of patients received sulfamerazine prior to the institution of penicillin therapy. Of these sixty-seven patients, twenty-six recovered and forty-one died—a recovery rate of 39 per cent. Thirteen of the patients were treated with a combination of penicillin and sulfadiazine. Of these, five recovered and eight died. The factors contributory to the difficulty of successfully treating pneumococcic meningitis include the presence of primary foci of infection which are frequently inaccessible; presence of bacteremia in many instances, and the occasional appearance of the disease in a fulminating form. All of the patients received penicillin intraspinally following the removal of an equal or somewhat larger amount of cerebrospinal fluid. The sodium penicillin was dissolved in isotonic solution of sodium chloride in a dilution of 1000 units per cc. The intrathecal dosage varied from 5,000 to 25,000 units and was administered at twelve- or twenty-four-hour intervals. In a few instances, the drug was also administered intracisternally or interventricularly, and in two cases subdurally. Intrathecal administration of penicillin was continued for a varying number of days after clinical improve-

ment was manifest and the spinal fluid no longer showed organisms or diminution in the sugar content. The total intraspinal dosage varied from 10,000 to 700,000 units with an average of 175,000 units. They conclude that while penicillin was highly effective in the treatment of an appreciable number of cases, it proved ineffective in a majority of instances.

Applebaum<sup>38</sup> concludes that in this type of meningitis it is advisable to employ chemotherapy in conjunction with penicillin. Sulfadiazine is the drug of choice and should be given in the manner described by him in the treatment of meningococcic meningitis. It is important to continue the combined therapy for at least a week after the patient has been well clinically, the spinal fluid has become sterile, and the fluid sugar has returned to normal. He does not recommend the use of type specific serum in this condition. He emphasizes that complete eradication of the primary foci of infection is of the utmost importance in the treatment of this form of meningitis. Sweet and his colleagues<sup>42</sup> report their experiences with the use of penicillin in the treatment of sixteen patients having pneumococcic meningitis, and compare the results with those obtained in forty consecutive patients treated with sulfadiazine or sulfamerazine. In the first group there were nine deaths. Among the patients treated with the sulfonamides alone there were thirty-seven deaths. The two groups were shown to be very similar as regards to factors which are important in the evaluation of the prognosis. The duration with penicillin varied from 12 to 108 days in the recovered patients. They conclude that the optimal treatment of pneumococcic meningitis should include both penicillin and sulfadiazine or sulfamerazine. The penicillin should be given both intra-

thecally and systemically. They advise penicillin to be administered intramuscularly or intravenously at the rate of 200,000 or more Oxford units per day so that intrathecal penicillin therapy may be reduced to a minimum. In this way the intrathecal dosage can probably be kept as low as 10,000 to 20,000 Oxford units per day. In order to reduce irritation further, this dose should be diluted in 20 to 30 cc. of isotonic solution of sodium chloride.

Boyette and Venning<sup>43</sup> report four cases of pneumococcic meningitis in children with two recoveries. They believe this type of meningitis in children is best treated with sulfamerazine in a dosage sufficient to obtain blood concentrations of 12 to 15 mg. per 100 cc. penicillin, both intramuscularly and intrathecally, and type specific antipneumococcus rabbit serum in infants and in older children who do not respond readily to combined sulfonamide-penicillin therapy.

**Streptococcic Meningitis** — Applebaum<sup>38</sup> emphasizes that this type of meningitis is most frequently associated with otitis media and mastoiditis. The etiological agent in most instances is the hemolytic streptococcus. In a small number of cases, the *Streptococcus viridans*, *Streptococcus gamma*, anaerobic and unclassified streptococci have been recovered. He prefers **sulfadiazine** in the treatment of this disease. It is particularly important to maintain a concentration of the drug in the blood of 10 to 15 mg. per 100 cc. The chemotherapy should be continued for from seven to ten days after the spinal fluid has become sterile and all clinical evidence indicates that the infection has subsided. **Penicillin** is used in conjunction with the sulfonamide drug. The method of using penicillin and the dosage should be the same as described by

this author in the treatment of pneumococcic meningitis.

White and his colleagues<sup>37</sup> treated five patients suffering from this condition. Only one of the five recovered. The single recovery occurred in an infant three months of age in whom meningitis developed secondary to bilateral otitis media. Penicillin was started soon after admission before the child received any form of therapy. For two days she received 100,000 units daily by equal two-hourly intramuscular injection. Thereafter for four days she was given 50,000 units by the same route. Ten thousand units were given intracisternally each day in conjunction with the systemic therapy. Systemic sulfadiazine was started on the fourth day of the penicillin treatment.

**Staphylococcic Meningitis**—This is much less frequent than the forms of meningitic already discussed. It may be a complication of staphylococcic bacteremia, or it may develop secondary to infections on the face, to osteomyelitis of the skull or spine, or to spinal epidural abscess. In most instances, the patients having this condition have not responded to chemotherapy.

White and his colleagues<sup>37</sup> believe that *penicillin* is far superior to other forms of chemotherapy in this type of infection. Four patients suffering from *Staphylococcus aureus* meningitis recovered from their acute infection with the use of *penicillin*. These patients had all received sulfonamides before the institution of penicillin, but progress was not considered satisfactory. The two adult patients were given 100,000 units of penicillin each day, first by the continuous intravenous route and later by intermittent intramuscular injection. Two children received 25,000 and 50,000 units respectively, each by the intramuscular route. Intrathecal therapy in the two children was given intraventricularly

through an operative cranial defect. One of the patients with a subdural abscess was given intracisternal therapy. One child who had osteomyelitis of the second lumbar vertebra did not receive any intrathecal therapy. His response was prompt and adequate to the systemic therapy. These authors conclude that intrathecal use of penicillin therapy does not seem harmful. They believe the intracisternal injection seems to be the most effective route of intrathecal administration. Their plan of management of purulent meningitis is outlined: (1) Prompt diagnosis and ample supportive therapy, including surgical intervention if indicated. (2) Two hundred thousand units of penicillin administered systemically each day by the continuous intravenous route during the acute phase of the disease and later by intermittent intramuscular injection as the infection is brought under control. (3) Ten thousand to 20,000 units of penicillin intracisternally once or twice a day. (4) Ample sulfadiazine or sulfamerazine therapy systemically to attain blood levels of over 15 mg. per 100 cc. (5) Continuation of intracisternal penicillin until four days after the spinal fluid has cleared and nuchal rigidity has begun to decrease, and of systemic penicillin therapy until seven to ten days after the disappearance of all signs of infection.

Applebaum<sup>38</sup> also recommends penicillin in the treatment of staphylococcic infections. In three cases of staphylococcic meningitis, he was able to obtain one recovery with its use. He advises the continuation of combined therapy of penicillin and sulfadiazine for two to three weeks after the meningeal infection has subsided. He again emphasizes the eradication of primary suppurative foci.

**Influenzal Meningitis**—Meningitis due to *H. influenzae* is essentially a dis-

ease of infants and children. The evidence points to the fact that this form of meningitis is usually a primary disease. H. influenzae meningitis has no relation to epidemic influenza, which is a disease of the respiratory tract due to a specific virus. In this form of meningitis, most workers feel that a combination of type specific antibody serum and sulfadiazine should be used. Applebaum<sup>38</sup> recommends the use of chemotherapy (*sulfadiazine*) and type B *anti-influenzal rabbit serum*. It is advisable, he states, to continue the chemotherapy for a period of seven to ten days following the appearance of definite clinical improvement, sterilization of the spinal fluid and return of the fluid sugar to normal. During the course of treatment, a concentration of the drug in the blood should be maintained at 10 to 15 mg. per 100 cc. The rabbit antiserum is specific to type b H. influenzae. Its potency is determined in terms of mg. of precipitable antibody nitrogen. He recommends the dosage schedule as outlined by Alexander (see 1945 SERVICE VOLUME of The Cyclopedia of Medicine, Surgery and Specialties). The writer has found it practical to administer 100 mg. of antibody when the spinal fluid sugar is 25 mg. or less per 100 cc., and 50 mg. of the antibody when the fluid sugar is more than 25 mg. The antibody is diluted in an amount of physiological solution of Ringer's solution equivalent to 10 cc. per kg. of the patient's weight and is given intravenously with the speed of the drip adjusted so that administration of the diluted serum is completed within two hours. In addition, he recommends large amounts of fluids preferably in the form of continuous infusion of saline in order to speed up the urinary secretion of the capsular substance of the organisms. Twelve hours after the administration of the antibody the ade-

quacy of the treatment is decided by examining the patient's serum for its ability to produce capsular swelling of a suitable suspension of H. influenzae. If within twenty-four hours the spinal fluid sugar has risen, no organisms are found by smear or culture, and the patient's serum causes capsular swelling in a dilution of 1:10, no further antibody is needed. When antibody excess is not demonstrable, an additional dose of 25 mg. of antibody nitrogen is administered and the patient's serum is retested a few hours later. In resistant cases it may be necessary to give 25 mg. of antibody intrathecally.

**Tuberculous Meningitis**—There is no specific treatment for this type of meningeal infection. The number of cases of tuberculous meningitis which have been seen to recover is extremely small. Jennings<sup>44</sup> reports two cases which recovered from this type of meningitis. In these two patients, tubercle bacilli were found in the cerebrospinal fluid during the illness. Both clinically were clear-cut cases of meningitis and the cerebrospinal fluid of each yielded confirmatory evidence of meningitis besides the presence of tubercle bacilli. Both patients became well enough to leave the hospital, and one of them is known to have remained well for more than a year. In this case, the meningitis, the author states, was beyond doubt due to tubercle bacilli of human type.

**Mumps Meningitis**—Meningitis is a rare complication of mumps. Its incidence varies from 0.15 per cent to 0.5 per cent in different epidemics. It usually appears within a week of the parotid swelling but may precede the parotitis or be the sole manifestation of the disease. Coe<sup>45</sup> reports a case of primary mumps orchitis with meningitis. The case presented the clinical picture of lymphocytic meningitis and epididymo-

orchitis in a young adult. The cerebrospinal fluid examination during the acute meningitis revealed the following findings: The cells per cu. mm. varied from 1300 to 2300; the cells were predominantly lymphocytes. The protein varied from 80 to 100 mg. per 100 cc. The chlorides varied from 710 to 700 mg. per 100 cc. The sugar content varied from 50 to 55 mg. per 100 cc. There were abnormalities of the colloidal gold curve determinations of an indefinite nature.

**Salmonella Meningitis**—*Salmonella panama* is a subgroup of the typhoid-paratyphoid group of bacteria. Wood and Mayfield<sup>46</sup> report two cases of meningitis due to this organism. Invasion of the human meninges by this bacteria is not common. These cases are of interest, as the source of the infection was traced to an attendant in the milk laboratory of the hospital in which the babies were born, and because one survived with sulfadiazine therapy. In the infant who recovered, the daily dose varied between 1 and 1.5 gm. to maintain a blood level of 6 to 10 mg. per 100 cc.

**Torula Meningitis**—It is not known why the human body is not more frequently invaded by the widely disseminated yeastlike organism *Torula histolytica*, but no doubt, as in bacterial infections, disease depends upon the virulence of the invader as opposed to the resistance of the host. Less than half the cases reported have been recognized before death. It has been mistaken for tuberculous meningitis, brain tumor, encephalitis, lymphocytic choriomeningitis, and dementia paralytica (see 1945 SERVICE VOLUME of The Cyclopedia of Medicine, Surgery and Specialties). The disease has been considered invariably fatal although an apparent cure has been reported in one case treated with sulfadiazine. Jones and Klinck<sup>47</sup> report a fatal case as well as their studies of the

therapeutic effect of sulfadiazine on experimental infection in mice and the effect of sulfadiazine and penicillin on the organism *in vitro*. They found that gentian violet or thymol had no therapeutic value in their case. Experiments *in vitro* failed to demonstrate any growth-inhibiting effect of sodium sulfadiazine or penicillin on *torulae* nor did sodium sulfadiazine have any value in experimental mouse infection.

**Lymphocytic Meningitis**—Applebaum and his co-workers<sup>48</sup> review seventy-two cases of lymphocytosis in the cerebrospinal fluid caused by a variety of etiologic agents. The two most commonly encountered diseases were mumps meningoencephalitis (41.6 per cent) and acute benign lymphocytic meningitis, cause undetermined (23.6 per cent). In mumps meningoencephalitis with cerebrospinal fluid lymphocytosis, the onset was usually acute and occurred about four or five days after the first signs of parotitis. On two occasions, meningitic signs appeared a few days prior to evidence of a parotid gland involvement. Frontal headache was the most common complaint, and this was followed in order of frequency by increased feverishness, vomiting, nausea, dizziness, and nervous irritability. One patient had mild convulsions which subsided quickly. The average cell count of the spinal fluid was 298 per cu. mm. (80 to 100 per cent lymphocytes) during the peak of the illness. Other studies of the fluid were normal except for an occasional increase of proteins. Syphilis, tuberculosis, chemical irritation (intrathecal injection), tetanus, cysticercosis of the central nervous system, rabies, lymphocytic meningitis associated with malaria, and infectious mononucleosis were some of the causative agents of cerebrospinal lymphocytosis. As a clinical aid in a differential diagnosis of cases with lymphocytosis in

the cerebrospinal fluid, they offer the following classification:

1. Acute lymphocytic meningitis (benign):
  - (a) Acute lymphocytic choriomeningitis.
  - (b) Lymphocytic meningitis due to allied viruses.
  - (c) Aseptic meningitis, cause undetermined.
2. Other diseases of virus origin.
 

Mumps, acute encephalitis (varieties), poliomyelitis, rabies, herpes (zoster and simplex), the common contagions, postvaccination, lymphogranuloma venereum, infectious mononucleosis, Guillain-Barre syndrome, etc.
3. Specific bacteria:
 

Tuberculosis, syphilis, tetanus.
4. Fungi and parasites (uncommon):
 

Torula infection, cysticercosis, etc.
5. Chemical factors (intraspinal injections):
 

Serum, novocaine solution, lipiodol, etc.
6. Meningitis sympathica (irritative):
 

Sequela to trauma of brain, aural infection, subdural abscess, epidural abscess.

**Benign Lymphocytic Choriomeningitis**—Avery<sup>49</sup> reports four cases of benign lymphocytic choriomeningitis. He states that beside the classical form of meningeal involvement, cases showing evidence of encephalitis are encountered. Other cases have been described in which the syndrome corresponds to that of meningoencephalomyelitis. General malaise, headache, fever, and stiffness of the neck are always present. The usual clinical picture is that of a mild meningitis having a more or less sudden onset during or following symptoms of a mild upper respiratory disorder. The changes in the spinal fluid are confined to the cells, globulin, and pressure; the sugar and chloride content are normal. Lymphocytosis in the cerebrospinal fluid may vary from 30 to 1500 cells per cu. mm. The course is usually mild and recovery is the rule; however, deaths may occur. While it is probably true that the most frequent cause of benign lymphocytic

choriomeningitis is a specific virus, it should be borne in mind that the classical clinical syndrome can be produced by other pathological agents.

Toomey<sup>50</sup> emphasizes that a stiff neck may not always indicate that the meninges are irritated, nor does the absence of a stiff neck always rule out a meningitis. It is a sign, which, if present without other signs of meningeal irritation, may usually be ignored. He points out that a patient with a slow meningeal bleeder, one with a rupture berry aneurysm, or ruptured basal vessel, if not killed by the condition within a short time, may have nothing beside headache and an extremely stiff neck. The stiffness becomes more pronounced if bleeding persists. Other signs help out, such as signs of intracerebral pressure and gradual onset of unconsciousness. A lumbar puncture helps to make the diagnosis definite.

### Migraine

Butler and Thomas<sup>51</sup> present their preliminary observations on the use of intravenous *histamine* in the treatment of migraine. They report that thirty-four patients with severe migraine were treated with this form of therapy. Seven were improved and twenty-four became symptom-free. The patients were treated by the intravenous injection of 1 mg. of histamine as 2.75 mg. of histamine acid phosphate. This was diluted in 500 cc. of isotonic solution of sodium chloride and injected very slowly. The speed of injection usually started at about 5 drops per minute, the rate being increased as rapidly as was tolerated by the patient. Too rapid an injection resulted in, first, a flushing of the face, often tachycardia and finally a typical severe headache which could be relieved by slowing the rate of injection or the administration of epinephrine or ascorbic acid. The entire



injection usually took from four to eight hours. The blood pressure was taken hourly and any decided drop was considered an indication for cessation of treatment. The authors feel that histamine should not be given to patients with peptic ulcer or vascular disease.

Horton and his co-workers,<sup>52</sup> in a preliminary report, state their results with a new product for the treatment of migraine. The effect of the new drug, D.H.E.-45 (*dihydroergotamine*) was studied in 120 patients. This drug is said to possess experimentally a marked sympathicoparalytic action similar to *ergotamine tartrate* and to be eight to ten times less toxic in cats and dogs than ergotamine tartrate. Its vasoconstricting effects are of shorter duration than ergotamine tartrate. Of the entire group of 120 patients, only 8 (7 per cent) experienced toxic reactions from the new drug. Of these 8, 4 exhibited nausea and vomiting, 2 reported general malaise, and 1 pain in the legs. Several patients received daily injections for weeks; others used the drug at intervals over three and one-half years without evidence of toxicity. The authors conclude that D.H.E.-45 was just as effective as ergotamine tartrate in the relief of acute attacks of headache. Neither drug prevented the occurrence of future attacks. Toxic reactions were noted to be three times more frequent with the use of ergotamine tartrate than with D.H.E.-45.

Palmer<sup>53</sup> reviews the subject of migraine in a comprehensive paper in which he concludes the most satisfactory drug for the relief of the pain of migraine headache is *ergotamine tartrate*. Most patients are relieved of the excruciating pain in from forty to ninety minutes, after hypodermic or intramuscular injections. The dose employed was usually 0.5 cc. (0.25 mg.) or 1 cc. (0.50 mg.) of ergota-

mine tartrate (gynergen) in a 1:2000 solution. In instances where reliance on ergotamine tartrate was absolutely essential and in which the side effects, especially the gastrointestinal symptoms, were distressing or alarming, he employed an additional small dose of *atropine sulfate*, 0.2 to 0.4 mg., or *bellafoline*, 1 cc. (containing 0.5 mg. calculated at L-hyoscyamine) by hypodermic or intramuscular injections. He has had disappointing results with the inhalation of pure oxygen given at the inception of the attack. Rectal suppositories containing an analgesic and sedative combination have been helpful in cases where persistent vomiting had prevented oral administration and where hypodermic injection was unwise or inconvenient. The author has studied the effects of intensive *vitamin B* complex therapy in the treatment and prevention of this condition. The method used was as follows: In severe cases, *i. e.*, those averaging ten or more days of headache a month, the medical program called for 100 mg. of *thiamin chloride* by intramuscular injection daily, 50 mg. of *nicotinic acid* (orally) three times daily after meals, *vitamin B* complex syrup in doses of one tablespoon twice daily, and *pyridoxine hydrochloride*, 15 mg. in tablet form, once daily.

In milder cases, the doses were diminished in size and frequency. For example, in a moderately severe case averaging one or two attacks a month, with a total of three or four days of headache a month, the treatment consisted of 100 mg. of thiamine chloride by intramuscular injection three times weekly, nicotinic acid, 25 mg., by mouth after each meal, and the same dose of vitamin B complex. The treatment was continued for a minimum of four months and then, if results justified reduction of dosage, the size and frequency of the

doses were decreased gradually. If, during the therapy, the patient experienced a threat of impending migraine, he was given 100 mg. of thiamine chloride intramuscularly in addition to the regular dose and was instructed to take 100 mg. of nicotinic acid after each meal on that day. The extra doses were continued until the threatened attack was liquidated. The results with this method of vitamin B therapy were considered very satisfactory. In a series of 500 cases, approximately 65 per cent experienced complete relief, an additional 20 per cent were benefited in degrees varying from 30 to 90 per cent. Two cases in this series had allergic reactions to the intramuscular thiamine chloride.

Among the newer therapeutic agents employed has been *octin (methyliisooctenylamine)*, which was given orally as octin mucate and by intramuscular injection in the form of octin hydrochloride. It appears to act by direct relaxation of smooth muscle and by stimulating the sympathetic inhibitory fibers innervating the smooth muscle. In this sense its physiological action resembles that of ergotamine tartrate, which depresses or paralyzes the motor sympathetic. The method employed in the treatment was as follows: One tablet (0.13 gm.) of octin mucate (2 grains) was given orally two or three times daily for periods of weeks or months. If a threat of migraine headache occurred, 1 cc. of octin hydrochloride in an aqueous solution (100 mg.) was given by intramuscular injection. This dose could be repeated in two hours if the headache did not become aborted or materially diminished. The results in a series of twenty-seven cases, he feels, have been encouraging, in that it seems possible to prevent regularly recurring migraine episodes by the oral administration alone in about 60 per cent of cases and to cut short or entirely eliminate

impending migraine attacks in about half the cases. The use of the drug is still in the experimental stages.

According to Palzer and his associates,<sup>54</sup> because of its prolonged action, it was thought that *eucupine* (isoamylhydroprene) might prove useful in periarthral infiltration for the relief of migraine. As described by the authors, the technic of infiltration is simple. The superficial temporal artery of the involved side is located external to the zygoma and approximately 2 cc. of 0.1 per cent eucupine in 1 per cent of procaine solution is injected. Often it is necessary to inject subsidiary painful points which are discovered by palpation. The results as reported were beneficial in two ways: The majority of patients had immediate relief (though failures were encountered), and the frequency of attacks were decreased as a rule.

It has been observed that patients with migraine may report that after the first hour or two of the attack the quality of the headache may change in that the initial pulsating or throbbing headache becomes a steady ache. To account for these changes, Torda and Wolff<sup>55</sup> have postulated that, after sustained dilatation of the cranial arteries, there occurs thickening or edema of the muscular and adventitial structures. Sections taken from the temporal arteries of patients during attacks of migraine involving this structure revealed on microscopic study that there was thickening of the arterial walls. Since comparable controlled sections during periods of freedom from headache could not be obtained, the authors studied the structure of the arteries of the ears of six cats after infusion for two hours of 10 cc. of isotonic solution of three chlorides containing 0.5 mg. of acetylcholine bromide per 100 cc. Measurements demonstrated thickening of the walls of the infused vessels. Er-

gotamine tartrate was less effective in constricting the arteries with thickened walls than arteries with normal walls. They suggest that during attacks of migraine the cranial arteries involved may undergo similar changes after prolonged vasodilatation. Such changes may explain the rigid pipelike texture of the arteries, the steady aching pain and tenderness of these structures when headache has persisted for many years. Also these changes may explain the decreased ability of ergotamine tartrate to reduce promptly the intensity of prolonged headache.

Williams<sup>56</sup> describes the syndrome of what he terms physical or intrinsic allergy of the head (myalgia of the head). He believes this is a specific type of headache which must be distinguished from migraine, glossopharyngeal neuralgia, and psychogenic headache. The diagnostic criteria for myalgia of the head are: (1) As a rule, it appears in the third decade of life or later; (2) it is likely to appear after an acute infection; (3) this is so because sensitization to physical agents is more readily accomplished in the presence of acute infection; (4) patients report precipitation of symptoms on exposure to physical stimuli, such as drafts, changes in temperature, changes in atmospheric pressure, to emotional stimuli, particularly anxiety condition states; (5) characteristics of myalgia are circumscribed localization of tenderness to attachments of certain definite muscles to the cranial bones, origins of certain muscles from the cranial bones and tender stiffened parts in the belly in the involved muscles; (6) the involvement is usually unilateral but may be bilateral; (7) the pain is of the deep and smooth type, and tends to be referred to a distribution which is not that of spinal roots. This referred pain often can be reproduced by pressure on the tender

origins or by the injection of hypertonic saline solution or histamine into the involved part of the muscle; (8) associated with the myalgia in certain instances is neuralgia of one or more branches of the fifth cranial nerve on the same side; (9) in certain cases, evidence of vasodilatation, mucoid nasal secretion, tinnitus, vertigo, and the like may be present on the homolateral side during the attack. The author describes his treatment based on a concept that there is a physical allergy involving muscle, called myalgia of the head, present in many patients who complain of headache. The writer utilized the injection of nicotinic acid daily. The initial dose was 25 mg. of nicotinic acid. This was increased by that amount daily until a dose which relieved symptoms was reached. This usually proved to be 100 mg. daily by hypodermic injection. It was found when the same dose could be given by mouth night and morning, it usually maintained this relief. After two or three months of daily treatment with niacin, it was found that relief could be continued when 100 mg. of niacin was administered by mouth three times a week. He states that fifty-four of the seventy-two patients who were treated with this regime obtained relief.

### Multiple Sclerosis

Rucker<sup>57</sup> again emphasizes the fact that patients afflicted with multiple sclerosis present, on ophthalmoscopic examination, a peculiar white sheathing of some of their retinal veins. In certain instances, it appears as a thickening of the walls of the veins, especially in their peripheral branches. In other instances, it takes the form of small white plaques overlying the veins, and there occasionally may be a constriction of the caliber of the lumina. Thickening of the walls away from the disk is almost always in-

dicative of disease. In a series of fifty cases observed for this phenomenon, multiple sclerosis was present in thirty-one cases; it was suspected in eleven and was absent in eight. This author believes that retinal perivenous sheathing occurs at any age and during any time in the course of multiple sclerosis and is not related to visual difficulties. He believes that its incidence in this disease may be close to 20 per cent. He concludes that sheathing of some of the retinal veins is occasionally encountered on ophthalmoscopy of otherwise normal ocular fundi, but it is usually indicative of disease of the central nervous system, most often of multiple sclerosis.

Veasey<sup>58</sup> considers the early ocular symptoms of multiple sclerosis. In his experience the earliest ocular symptoms consisted of a transitory disturbance of central visual acuity. The patients complain of obscuring of central vision. These symptoms disappear in a few days. Subsequently, there may be a central or paracentral scotoma, revealed only by the use of a small test object. The scotoma may be relative or absolute. It may be permanent or disappear with the visual symptoms. In some instances, pain is observed on pressure or movement of the eyeball. In a certain proportion of cases, he found a sheathing of portions of the retinal veins, with normal arteries. There were cases in his series in which there was a sudden onset of blindness associated with a rapidly enlarging central scotoma. These visual symptoms and signs may be present for a long time without the presence or appearance of some of the classical pathognomonic features of the disease.

Nielsen,<sup>59</sup> in a comprehensive review, discusses the problem of multiple sclerosis. He emphasizes the fact that the prognosis of multiple sclerosis is not always bad. The symptoms may be mini-

mal and may never become incapacitating. In cases with an acute course, the prognosis is usually said to be bad, but an occasional patient with acute multiple sclerosis has survived. The duration of life from the time diagnosis is possible ranges from a few months to thirty years; the average is probably fifteen to twenty years. He admits that he finds it difficult to evaluate the various forms of treatment for this condition. He states that Brickner's ideas concerning the intake of certain foods, especially dairy fats, should be followed when possible. He concludes that it is too early to arrive at a definite opinion as to the value of intravenous infusion of *histamine* diphosphate as advocated by Horton and his associates (see 1945 SERVICE VOLUME). The author prescribes all forms of *vitamin B* and occasionally gives transfusions of *whole blood* to stimulate reaction of the body to the disease. Women should be advised against pregnancy; however, he does not feel that women with multiple sclerosis should be advised against marriage.

### Myasthenia Gravis

Viets<sup>60</sup> reviews the clinical aspects of myasthenia gravis and evaluates his experience of nine years during which he has seen 125 cases at the Massachusetts General Hospital. Many hundreds of tests with the diagnostic ampoule (1.5 mg. of *neostigmine methyl sulfate* with 0.6 mg. of *atropine sulfate*) have confirmed the original observations that neostigmine is a specific antidote for the curarelike symptomatology of myasthenia gravis. He found that a few other diseases respond in a minimal fashion to the parenteral neostigmine, such as amyotrophic lateral sclerosis, bulbar palsy, and some of the muscular dystrophies and syndromes of a similar

nature. He does not believe it is necessary to use curare or quinine in the establishment of the diagnosis of myasthenia gravis as the diagnosis can usually be made by history, and injection of neostigmine. He emphasizes that the use of the fluoroscope to study the swallowing reflex before and after neostigmine injection is one of the most valuable means of establishing the diagnosis. If, after the neostigmine sulfate is given, the patient is allowed to swallow normally, without retention of barium in the throat, the diagnosis of myasthenia gravis cannot be questioned. Such a result does not occur in bulbar palsy. He reviews his program of treatment in these cases and emphasizes the fact that the drug must be so administered orally that a neostigmine level will be maintained during the entire twenty-four hours. Some patients are maintained on a minimal amount. In a few cases, as little as 15 mg. divided into two doses taken by mouth is able to relieve mild symptoms. The average intake of forty-five ambulatory patients was 10.9 tablets of neostigmine bromide, 15 mg. each, spaced during the twenty-four hours, or a total of 163.5 mg. The highest dosage was 5 tablets a day for a patient who had been maintained on this intake for a number of years. The spacing of the drug during the twenty-four-hour period is of considerable importance. Information in regard to the hourly needs can be obtained from the patient by the use of a chart on which the patient records his state of health four times a day. When a patient is more seriously ill, neostigmine is of necessity given in the form of neostigmine methyl sulfate by subcutaneous or intramuscular injection. The subcutaneous dosage is satisfactory and, because of this, the patient can be trained to give the injection himself, similar to the procedure adopted in the

treatment of diabetes. Ephedrine sulfate is a useful adjunct to neostigmine in the treatment. Its effectiveness is about 10 to 15 per cent of that of neostigmine. It is possible to maintain a few patients entirely on ephedrine sulfate if the symptoms are not very severe. Ordinarily, ephedrine sulfate is added in doses of 24 mg. two or three times a day to the regular neostigmine schedule. About half of the patients under observation have found the drug useful for this purpose and have continued to take it over a long period of time. The only caution usually needed with regard to this drug is in relation to its possibility as a cause of insomnia. For this reason the drug is usually not taken after 12 o'clock noon. **Potassium chloride** has a mild effect on the symptoms of myasthenia gravis. It is disagreeable to take. A few patients are able to take it in a 25 per cent solution dissolved in orange or tomato juice. **Guanidine hydrochloride** has a considerable effect on the symptoms of myasthenia gravis in some patients. One of his patients has taken nine tablets (125 mg. each) a day for many years with complete relief from her disability. Fifteen patients have been subjected to **thymectomy** (see 1945 SERVICE VOLUME) in the past four years. There have been four operative deaths; thymomas have been found in four patients, hyperplasia of the thymus was found in three, and the thymus appeared normal, although persistent, in eight other cases. Two are considered at the present time as in complete remission, two more are distinctly improved, three are moderately improved, one slightly improved, and three have been operated upon too recently to be evaluated. None of these patients had relapses. The following facts are produced by the study of post-operative patients: If the thymus shows

hyperplasia when removed, it does not necessarily mean that the patient will show improvement as the result of the operation. Four of the patients in the series had thymomas but it was not clear that they had done better than some of the patients with hyperplasia of the thymus, or, indeed, those whose thymus was normal. Viets concludes that he is not in a position at this time, from his experience, to advocate thymectomy in every case of myasthenia gravis.

Murray and McDonald<sup>61</sup> studied the thymus glands removed from 10 fetuses, and from 100 persons from the ages of four months to eighty-six years. They also studied thymomas associated with myasthenia gravis in 13 cases and 2 thymic tumors removed surgically from patients with myasthenia gravis. They conclude that the incidence of myasthenia among patients with thymomas

cases of the disease observed. Ocular symptoms or signs were present in all cases. Purely "ocular" myasthenia gravis was observed several times but in such cases there was always the possibility of a spread of the weakness. Ocular symptoms and signs usually appeared early in the course of the disease. Occasionally, they were a late development. Ptosis was the most constant ocular sign. Weakness of the orbicularis oculi may occur in the absence of ptosis or with it. Limitation of ocular movements occurs unilaterally or bilaterally and in almost all combinations. When pupillary abnormalities are present, it is doubtful if the case is one of myasthenia gravis. Visual fields and visual acuity are not altered.

Richter<sup>63</sup> presents the following table to indicate the effective drugs in the treatment of myasthenia gravis in order of their importance and usefulness:

<i>Drug</i>	<i>Dose</i>	<i>Use</i>	<i>Side Actions</i>	<i>Control of Side Action</i>
Prostigmine Hydrobromide (15 mg. tablet)	60 mg. to 200 mg. a day in 3 to 6 divided doses	Primary control of muscle weakness	Nausea Abdominal distention Cramps and diarrhea	Atropine .0007 gm. (1/100 grain) or Tr. belladonna 10-15 drops t.i.d.
Ephedrine Sulfate (capsules $\frac{3}{8}$ grain)	0.022 gm. ( $\frac{3}{8}$ grain) b.i.d.	Supplementary to prostigmine	Nervousness, tachycardia, insomnia	Reduce dose or change to another drug
Guanidine Hydrochloride (tablets 125 mg.)	10 mg. to 25 mg. per kilo body weight in 3 or 4 divided doses	Supplementary to prostigmine if ephedrine is not satisfactory	Gastrointestinal symptoms Nervousness and muscle twitching	Atropine Calcium Gluconate
Potassium Chloride	10 to 15 gm. t.i.d. in eggnog	Supplementary to prostigmine if ephedrine or guanidine is not effective	Gastrointestinal symptoms Diuresis	Bismuth Subsalicylate

is nearly 100 per cent. This is in variance with Eaton, who has stated that the incidence of thymomas among patients with this disease is 14 per cent.

Walsh<sup>62</sup> reviews the ocular signs of myasthenia gravis based on sixty-three

### Neuritis

Although pathologic conditions of the peripheral nerves have long been recognized, large gaps in our knowledge exist concerning the etiology and symptomatology of such conditions. Diabetic neu-

ritis or neuropathy has been considered by some to be the result of degenerative changes resulting from the disease of the peripheral arteries, by others the result of specific deficiency resulting from dietary modification.

Rundles<sup>63a</sup> reviews the subject based on the study of 125 cases in which the diagnosis of diabetic neuropathy was made. Most diabetic patients with disease of the peripheral nerves have apparently had neglected or poorly managed treatment. The disordered metabolism of diabetes seems to be the etiologic factor in this complication. Severe polyneuropathy was precipitated, sometimes acutely, after periods of neglect, by common infections, surgical procedures, and other events capable of aggravating the severity of the diabetes. Not only may the peripheral motor and sensory neurons be involved, according to Rundles, but also spinal nerve roots, autonomic pathways concerned with temperature regulation, postural blood pressure adjustment, vasomotor control, and intestinal and bladder function. He reports that he has not seen a patient in whom diabetic neuropathy actually preceded the appearance of diabetes mellitus. He finds that diabetic neuropathy tends to occur in patients with mild diabetes, many of whom have had neither diabetic acidosis nor coma, as well as in those with more severe diabetes. In twenty-five of his cases there had been no diabetic treatment at all before the hospital admission. Of the remaining patients who had some treatment, everyone seemed to have received only what would be called poor treatment. Liver enlargement was found in thirty-eight patients with diabetic neuropathy, excluding those with cardiac, biliary tract, and other recognized hepatic diseases. Among early symptoms were muscular cramps, aching, and muscular weakness, especially of the legs,

and these symptoms were characteristically made worse on exposure to cold and at night. The lower extremities were affected more severely, almost without exception. The peroneal nerve was more vulnerable than the tibial, the ulnar more vulnerable than the radial or median. Occasionally, symptoms occurred predominantly in the pudendal, femoral, or intercostal nerve areas, or asymmetrical areas in the extremities. With uncontrolled diabetes the tendency was toward increasing severity and persistence of symptoms. Diminished or absent tendon reflexes constituted the commonest neurologic abnormality. The cutaneous sensibilities were blunted peripherally in about half the patients. Pronounced muscle tenderness was present in forty-six cases. The vibratory sense at the ankles was diminished in thirty-seven patients and absent in twenty. Complete foot drop was present in ten cases. The abnormal pupils were, in most instances, myotic, reacting sluggishly to light, better on accommodation. Irregular and unequal pupils were observed. Thirty-nine spinal fluid examinations were made in thirty-one patients. Ten fluids were normal, while thirteen had excess total protein ranging from 40 to 80 mg. per 100 cc. Disturbed gastrointestinal function appeared to be a common accompaniment of diabetic neuropathy and one which the author, in view of the other evidences of disturbed autonomic nerve function, as well as the high incidence in the same patients of genitourinary and sphincter abnormality, considered the result of autonomic nerve disease. Thirty-two of the patients in this study had genitourinary and sphincter disturbances. Complete lack of sexual potency was recorded in nineteen patients, and this often preceded any other symptoms of peripheral nerve disorder. Eighteen patients were found

to have an atonic type of bladder paralysis. Cystometric examinations in thirteen of these showed impaired or absent sense of feeling, low expulsive force, and an increased bladder capacity. The sphincter disturbances appeared to be the result of involvement of the pudendal nerve. The bladder paralysis of diabetic neuropathy is an atonic neurogenic paralysis similar to that seen in *tabes dorsalis*, pernicious anemia with peripheral nerve and posterior column disease and alcoholic neuropathy. Some of the patients with diabetic neuropathy exhibited unusual degrees of peripheral sympathetic nerve damage, as revealed by sweating deficiencies, loss of vasomotor and pilomotor control, dependent edema, and certain types of skin alteration. This type of edema is presumably due to involvement of the vasomotor nerves. Defective orthostatic regulation of the blood pressure was found in eight of the patients. The blood pressure in the supine position was usually normal, but the systolic, and, to a lesser degree, the diastolic pressure declined precipitously on standing, causing faintness, dizziness, and syncope. The successful treatment of diabetic neuropathy requires expert diabetic management. Rundles found that administration of insulin was the most effective means in the control of this complication. He insists that it should be given at least for the duration of the active neuritic disease. Benefit was not observed from the addition of vitamins, and in particular of thiamin. A poorly understood and disturbing phenomenon encountered in the treatment of diabetic patients with associated neuropathy is the acute intensification of the neuritic disease which sometimes occurs shortly after control of the diabetes is undertaken. Neuritic disease may also appear for the first time in those with a history of prolonged diabetic neglect a few weeks

after treatment is begun. This study points out the association of diabetic neuropathy with chronic unregulated diabetes and suggests a metabolic cause, the nature of which, however, has not thus far been elucidated. The author emphasizes that diabetic neuropathy, as well as retinopathy and hepatomegaly in their early stages, are reversible changes, provided they are recognized early and are properly treated.

Rudy and Epstein<sup>64</sup> review 100 cases of diabetic neuropathy followed from one to ten years. The incidence, according to clinical localization, was neuropathy, 55 cases; myelopathy, 26 cases; encephalopathy, 4 cases; encephalomyelopathy, 4 cases, and neurogenic bladder disturbance, 11 cases. These authors state that diabetic neuropathy is a generalized neurologic disturbance. It is observed not only in the acute stage of diabetes but also soon after the control of the glycosuria and hyperglycemia and in the chronic and even mild cases of diabetes. The neurologic complication develops most frequently in patients over fifty years of age and is preceded or accompanied by a considerable loss of weight. Symptoms and signs of a vitamin B complex deficiency are frequently associated with it. The vitamin deficiency is secondary and it appears to be caused by the disturbed metabolism and at times being associated with a chronic infection or other complication. A demonstrable dietary insufficiency is a factor only in certain cases. Complete recovery from the neuropathy is certain and slow, but it occurs following prolonged therapy with vitamin B and control of the glycosuria and hyperglycemia.

Foster<sup>65</sup> describes the pathologic changes in the peripheral nerves in four cases of pernicious anemia in which necropsy was performed, and the results



of biopsy of a peripheral nerve in an additional case. The degeneration of the peripheral nerves was found in the four cases of pernicious anemia with posterolateral sclerosis in which necropsy was performed, and the biopsy specimen gave evidence of peripheral neuropathy. The degenerative changes in the nerves were less severe in the two cases in which liver therapy had been given and the patients were in hematologic relapse at the time of pathologic examination. It has been frequently observed that the improvement in neurologic function with *liver therapy* is greatest when there is a scarcity or absence of pyramidal tract signs. That is, when manifestations commonly assigned to dysfunction of the posterior columns predominate. Since such disturbances as ataxia, impairment in vibratory sensation, impairment in the sense of motion and position, diminished intensity or absence of deep tendon reflexes, and bladder dysfunction may be caused by degeneration of extramedullary nerve pathways, which possess a powerful regeneration capacity, it is suggested that the improvement with liver therapy is due to regeneration of peripheral nerves. An optimistic and aggressive therapeutic attack is therefore justifiable, particularly when there is a disorder in those functions shared by the peripheral nerves and the posterior columns of the spinal cord.

**Causalgia**—Burning pain, hypesthesia, and trophic disturbances, such as edema, glossy skin, and a local rise in temperature, resulting from injury to a peripheral nerve were first grouped as a symptom complex in 1813 by Denmark. In 1864, the term causalgia was coined by Mitchell, Morehouse, and Keen to describe the above symptom complex. Speigel and Milowsky<sup>66</sup> present a preliminary report of nine cases successfully treated by surgical and chemical inter-

ruption of the sympathetic pathway. In their unselected series of 275 peripheral nerve injuries, 9 presented a picture of causalgia. The syndrome followed injury to all or any of the major nerves of the upper extremity. In spite of numerous lower extremity nerve injuries, only one case of lower limb causalgia occurred. Injury to a blood vessel frequently accompanied nerve injuries in causalgia but was not a necessary concomitant of nerve injury in the production of causalgia. The most common symptom of causalgia was hot burning pain aggravated by movement and friction. The most constant findings were shiny, cold, profusely perspiring and frequently cracked skin in the involved extremity with hypesthesia occurring in most of the cases. Roentgenologic evidence of decalcification of the involved extremity was frequently seen. The pain did not appear to be due to the continuous irritation of scar or foreign body. The degree and quality of pain were in no way commensurate with the type and extent of injury. In none of the cases did the sensory deficit outline the area of causalgia but the two frequently shaded into each other. Personality disorders and hysteria were the result rather than the cause of causalgia. Neurolysis was not a useful procedure in the treatment of causalgia *per se*, although it was necessary in the treatment of the specific nerve deficit. Interruption of the sympathetic pathway temporarily by *sympathetic block* or permanently by *surgical sympathectomy* was a highly dependable form of treatment. In the upper extremity, it was not necessary to remove the stellate ganglion for effective control of the pain. Occasionally, the causalgic pain could be more or less permanently controlled by sympathetic block with local anesthesia where sympathectomy for other reasons

was not feasible. Alcohol block in selected cases was a useful procedure. deTakats<sup>67</sup> concludes that the causalgic state is due to a chronic irritation of sensory pathways producing cutaneous hyperalgesia, burning pain, and a local increase in blood flow. Three sensory levels, a peripheral, a spinal, and a cortical, can be recognized. The lesion becomes more and more intractable the higher it ascends. In the first stage, local infiltration and block of the paravertebral sympathetic nerves are effective. At the second level, anterolateral cordotomy has been most helpful. The treatment of the third stage was cerebral tracheotomy, where removal of the sensory cortex is still in its infancy. He emphasizes the fact that early diagnosis and immediate treatment save much suffering and eliminate permanent disability. The true hysterical lesion shows no vasomotor change except those due to immobility.

### Shoulder Girdle and Upper Extremity Pain

Love<sup>68</sup> reports on his experience with the scalenus anticus syndrome with and without cervical rib. He points out that cervical rib is of infrequent occurrence. Out of a group of over 500,000 patients, Adson and Coffey found 303 cases of cervical rib. In only 36 of the 303 cases were the symptoms sufficiently characteristic and of a degree severe enough to warrant surgical treatment. In 55 per cent of these cases, the anomaly was an accidental discovery because it did not produce symptoms. These authors, however, called attention to the important rôle of the scalenus anticus muscle in the production of the nervous and vascular symptoms and to their method of relieving the symptoms and signs by division of the scalenus anticus muscle. Some feel that the scalenus anticus muscle is the important offending structure

in the production in the syndrome of cervical rib. They are of the opinion that whether a cervical rib is present or not, the muscle produces compression of the subclavian artery and brachial plexus. Some are of the opinion that trauma is a factor in the production of the nervous and vascular symptoms referable to the subclavian artery and brachial plexus. They think that trauma, direct or indirect, to the scalenus muscle may result in fibrosis and contraction with subsequent compression of the nerve trunks and subclavian artery. Some suggest a theory of acute infection resulting in scalenus anticus myositis. The diagnosis of scalenus anticus syndrome is based on the history of pain, atrophy, circulatory abnormalities, disturbances of sensation, and paresthesia in the upper extremity and a reduction or obliteration of the radial pulse when the scalenus anticus muscle is put on tension, as in extending the neck with the head turned to the affected side while taking a deep breath. The pain is usually felt along the inner side of the arm in the course of the intercostal, cutaneous, ulnar, and median nerves. Occasionally, the pain may be widespread and distributed over the entire region supplied by the brachial plexus. Atrophy is usually a late occurrence. Circulatory symptoms are rarely severe but may be so. The finding of cervical rib either by palpation or roentgenologic examination is not sufficient evidence to warrant a diagnosis of the scalenus anticus syndrome since many patients who have cervical rib have no symptoms that can be ascribed to the ribs.

Wright<sup>69</sup> describes a neurovascular syndrome produced by hyperadduction of the arm. This is capable of producing severe vascular symptoms secondary to occlusion of the subclavian artery and neurologic sensory complaints, probably secondary to stretching, and ischemia of

the brachial plexus trunks. He describes four patients who developed their symptoms as a result of prolonged sleeping in the supine position with their arms hyperadducted; in each case, this resulted in arterial occlusion or stretching of the involved nerve trunks. In other cases, the syndrome developed as a result of occupational hyperadduction. He recommended that persons whose pulse can be occluded in the hyperadduction position refrain from sleeping or working with their arms in that position. LeVay<sup>70</sup> reports a case of compression of the subclavian vessel and brachial plexus by the clavicle and first rib, and emphasizes the fact that it is possible to get pressure on the brachial plexus and subclavian vessel by actual compression of a clavicle against a normal first rib. Scalenotomy would, of course, be pointless in such cases since these patients could only be relieved by partial resection of the rib concerned. This syndrome of costoclavicular compression of the brachial plexus and subclavian vessel may be a more common mechanism than one would suspect and would explain the failure of scalenotomy in certain instances. The clinical picture produced would be similar to that of a scalenus anticus syndrome. If costoclavicular compression is obvious and it is decided to resect part of the first rib, the plexus must be extensively mobilized since it is important to remove enough bone laterally. In costoclavicular compression, the symptoms are exaggerated when one tells the patient to brace his shoulders by the characteristic backward and downward movement performed in shoulder bracing. This maneuver approximates the clavicle to the first rib and would tend to exaggerate the subjective symptoms and signs of vascular obstruction.

Walshe and his colleagues<sup>70a</sup> report on their study and conclusions on the

pressure effects associated with cervical and with rudimentary and "normal" first ribs. They are of the opinion that an abnormal rib is never a solitary anatomical aberration, and that cases of abnormal rib associated with clinical symptoms should be primarily thought of, not in terms exclusively of the abnormal rib present but in terms of an abnormal upper thoracic outlet. The clavicle, they state, plays a significant rôle in the production of pressure symptoms in the presence of abnormal ribs. They describe a series of cases of cervical and rudimentary first rib pressure and the factors underlying the production of symptoms in these cases. "The factors are seen to be multiple — anatomical, pathological, and physiological. When an abnormal rib is present, it is rarely the only relevant skeletal abnormality, for scoliosis and vertebral deformities are commonly associated with it. The bony abnormality is therefore best expressed, not in terms of the abnormal rib alone, but in terms of an abnormal upper thoracic outlet. This outlet is commonly asymmetrical and abnormally raised and tilted. The nervous and vascular symptoms associated with this state of affairs are not, however, to be accounted for in terms of it alone, for there is evidence that the clavicle plays an important part in the compression of nerve roots and artery. The clavicle and the abnormal rib form the two arms of a vise in which these structures are recurrently compressed. This view does not exclude the rôle of a rib in exerting traction upon, stretching and angulating of, the structures which cross it. Secondary and pathological factors, arising from the maladjustment of bones and soft tissues, contribute an important part of the symptomatology. Damage to the subclavian artery may lead to its aneurysmal dilatation, with or without the formation of clot within it.

Thrombosis, when it occurs, leads to severe ischemia in the upper limb and sometimes to the production of emboli which lodge in the digital arteries and give rise to those gangrenous patches, sometimes erroneously attributed to disorders of sympathetic innervation. In fact, the various syndromes arising in association with cervical and rudimentary first ribs can only be accounted for when all these factors are taken into account, and this applies to nervous as well as to vascular symptoms.

"Reasons are given for concluding that vascular symptoms in the upper limb are not due to disorders of sympathetic innervation, but to mechanical interference with the blood flow through the subclavian artery. When true symptoms of sympathetic paralysis occur, they are referable to the stellate ganglion. Of the components of the syndrome of a paralyzing lesion of this ganglion, Horner's oculopupillary syndrome is the most familiar. In one case here recorded, other components were also present, and it is probable that systematic study of sympathetic functions in cases of rib pressure would reveal their presence more often. The stellate ganglion is probably involved in the inflammatory fibrous tissue reaction which occurs round the subclavian artery, but other ways in which its function might conceivably be affected are discussed.

"The factors leading to pressure symptoms affecting nerves and artery when no abnormal costal element is present: The so-called 'normal first rib' and 'scalenus anticus' syndromes are discussed. Perhaps the essential factor is a dropping of the shoulder girdle. This leads to increased tension on nerve roots and subclavian artery and, by narrowing the space between first rib and clavicle, probably leads to the compression of these structures by the clavicle during

movements of the arm. The action of scalenus anticus as an operative factor is problematical, and not of primary importance, and the title 'scalenus anticus syndrome' is seen to embody a hypothesis that is not adequate to account for the facts of observation."

They stress the importance of a more systematic radiographic study of the components of the upper thoracic outlet in all suspected cases of rib pressure.

Elliott and Kremer<sup>71</sup> report eight cases of brachial pain caused by herniation of the sixth cervical intervertebral disk. These patients demonstrated a uniform distribution of pain in the back of the shoulder, down the back of the arm, and the radial border of the forearm, and sometimes in the upper pectoral region. There were paresthesias in the thumb, index, and middle fingers. In some cases there was a history of acute stiff neck. The signs include limitation of movement of the neck, pain produced in the arm by movements of the neck and by downward pressure on the head, and tenderness, weakness, and wasting of the pectoralis major, triceps, and extensors of the wrists and fingers. The triceps jerk was reduced or absent and there was usually hypalgesia of the thumb and index finger. The clinical picture was that of a lesion of the seventh cervical root. Trauma was not an essential precursor of the syndrome and even when present it was not necessarily more severe than the minor traumata which may happen to anyone. Contrast myelography in three cases showed a filling defect opposite the sixth intervertebral disk, involving the seventh cervical root on the affected side. Treatment was conservative in this series of cases. However, the authors conclude that if conservative measures of head fixation and traction do not succeed in eliminating the pain, surgery is indicated.

<i>Mechanical</i>	<i>Traumatic</i>	<i>Disease</i>
1. Faulty posture	1. Acute and chronic strains (ligamentous or muscular) a. sacroiliac strain b. lumbosacral	1. Arthritis a. osteoarthritis b. rheumatoid (spondylitis deformans)
2. Scoliosis, functional and structural	2. Contusions	2. Fibrositis
3. Kyphosis, juvenile epiphysitis	3. Fractures and dislocations	3. Osteomyelitis a. tuberculous b. pyogenic
4. Congenital anomalies of the lumbosacral area a. spondylolysis b. spondylolisthesis c. asymmetry of articular facets d. sacralization (unilateral) e. spina bifida	4. Ruptured intervertebral disks	4. Tumors a. primary b. metastatic  5. Poliomyelitis 6. Syphilis

Speigel and Lewin<sup>72</sup> report three cases of surgically proved nerve damage following use of a rubber tourniquet. Tourniquet paralysis has been previously reported with some of them being permanent in nature. Apparently severe damage of peripheral nerves can occur as a result of application of a rubber tourniquet for surgical ischemia. Factors involved in the production of the paralysis are (1) pressure necrosis at the site of tourniquet application with fibrosis and production of neuromas; (2) ischemia below site of application of tourniquet with death of the ischemic portion of the nerve, fibrosis, and production of a neuroma in continuity; and (3) a combination of the foregoing two situations. The radial and sciatic nerves are the most vulnerable to tourniquet paralysis. The authors suggest that every case of tourniquet paralysis of a peripheral nerve immediately on its discovery should receive intensive physical therapy over a period of eight to twelve weeks.

If, at the end of this time, no appreciable return of function is evident, surgical exploration of the involved nerve should be performed and a neurolysis and neurorrhaphy should be attempted.

**Low Back Pain and Sciatic Syndrome** — Alpers<sup>73</sup> emphasizes the fact that although primary neuritis is a rare cause of sciatic pain it does not necessarily follow that herniated nucleus pulposus is the most common cause of sciatica. Secondary sciatica is much more common in the causation of the sciatic pain than is sciatic neuritis, but there are many causes of sciatic pain which cannot be disregarded, although they may be less common than herniated nucleus pulposus. Unfortunately, the history of a case of sciatic neuritis is similar in many details to that of secondary sciatica, particularly with reference to the occurrence of remission of pain. The onset in both neuritis and secondary sciatica may be acute or gradual, but a history of direct or indirect injury, of accessory symp-

toms referable to the spinal cord or its roots, of malignancy, arthritis, or other factors makes the differentiation clear in many instances. Sciatic neuritis is always associated with nerve trunk tenderness and responds to medical treatment.

Hochwalt and his colleagues<sup>74</sup> present an outline for the investigation of low back pain. They outline the common intrinsic causes of low back pain as shown on previous page.

### Neurological Complications of Other Diseases

**Uremia**—Uremia, although usually treated by the internist, occasionally results in symptoms that may cover the entire field of neuropsychiatric symptomatology. Knutson and Baker<sup>75</sup> have made a clinicopathologic study of the central nervous system in uremia. The most common symptoms referable to the central nervous system are convulsions and coma, but in isolated cases syndromes, such as monoplegias, hemiplegias, aphasias, apraxias, and mental symptoms of almost every type may be present. The studies by these authors reveal widespread tissue changes involving both the nerve cells and the parenchymal elements. In the acute illness, the predominant alteration occurs in the cortical neurons which reveal an acute change in the nerve cells. In the more chronic illness, the most striking changes are parenchymal rather than neuronal and consist of focal and perivascular areas of demyelination and necrosis. The neurons show both acute and chronic changes in the more chronic illnesses.

**Malaria**—Fitz-Hugh and his associates<sup>76</sup> report statistical data on 140 cases of cerebral malaria. These cases constituted 2.3 per cent of the total series of 6059 cases of malaria. Cerebral malaria was chiefly the result of *P. falciparum* infection. The cerebral

phenomena resulting from plugging of the capillaries by plasmodium, pigment-laden leukocytes, and erythrocytes varied from minimal to most violent. Cortical irritation, subcortical, brain stem, basal ganglion, frontal lobe, parietal lobe, cerebellar and hypophyseal syndromes were observed with or without the phenomenon of generalized cerebral edema. Photophobia and vertigo were frequent complaints. A moderate number of patients developed sudden severe cerebral symptoms one to three days after admission with what appeared to be ordinary malaria. Not uncommonly, there was a moderately stiff neck without Kernig's or Babinski's sign, and with absent knee jerks. Other cases had transiently positive Kernig's and Babinski's signs, exaggerated knee jerks and abortive clonus with or without stiff neck. These patients were treated as medical emergencies. If oral quinine therapy and oral fluids were not possible, the nasal catheter route of administration of *quinine, atabrine, fluids, salt, and sugar* was useful in many cases. Transfusion of *blood* or *plasma* brought a number of patients out of coma and caused the disappearance of pulmonary edema and seemed to make a difference of life and death. An initial spinal tap was done in comatose patients or those with stiff neck. The intravenous administration of epinephrine proved of value to certain comatose patients. The authors used total doses of 3 to 4 gm. of quinine each twenty-four hours in cerebral malaria. This was maintained for two or three days, then reduced to about 2 gm. daily until the patient was out of danger of relapse. A few cerebral cases were treated and cured solely with *atabrine*. For the maniacal or convulsive patient, intravenous *sodium amytal* was useful.

**Porphyria**—Porphyria, although a relatively rare condition, is of interest to

the neuropsychiatrist because it frequently results in extensive damage to the central nervous system. The central nervous system involvement may comprise the predominant symptomatology, often obscuring the fundamental nature of the disease process. The clinical picture of porphyria is variable and is confused with a variety of other well-known neurological disorders from which it must be differentiated (see 1945 SERVICE VOLUME). The most frequently affected structure seems to be the peripheral nerves, resulting in the development of motor weakness primarily of the lower limbs. The weakness is flaccid in type and usually ascends slowly to involve the upper extremities. In fatal cases, the disease process may ascend to the brain stem resulting in dysphagia, dysarthria, and finally in death from medullary paralysis. Baker and Watson<sup>77</sup> report the clinicopathologic studies of such a case. Their review of the literature reveals that the entire nervous system may be involved structurally in porphyria. In their case, neuronal and myelin sheath alterations were observed throughout the brain and spinal cord in addition to characteristic peripheral nerve changes.

**Complications Following Use of Vaccine**—Peacher and Robertson<sup>78</sup> report the neurologic complications following the use of typhoid vaccine. They indicate that neurologic complications are much more frequent following subcutaneous use of typhoid vaccine in immunization than is supposed, and may involve either the central or peripheral nervous system. The complication occurs within two to three weeks following any injection and is not dependent upon whether or not the patient has had a series of typhoid inoculations previously. The spinal cord and peripheral nerve pathology offer a more favorable prognosis than cerebral complication. They report

two cases. In the first, degenerative changes in the brain complicated its use intravenously in nonspecific protein therapy for chronic gonococcal urethritis. The second case presented a peripheral nerve paralysis following subcutaneous use of typhoid vaccine in immunization. Thomas<sup>79</sup> reports a case of ascending Landry's paralysis following antirabies vaccine. It has been estimated that about 3 in 10,000 patients who receive antirabies vaccine develop some sort of neuronal complication. The commonest form of paralysis, except the very mild ones, is one which resembles the ascending type described by Landry. The author observed this type of paralysis in a man who developed a reaction after the second injection of rabies vaccine. He developed a paralysis which was rapidly progressive, so that within four days he had a complete quadriplegia. There was some muscle soreness in both upper and lower extremities, but otherwise no sensory changes. The progress in this case with intensive supportive treatment was encouraging. At the time of the report he could walk without crutches and could hold light things in his hands.

**Spinal Anesthesia**—Yaskin and Alpers<sup>80</sup> review the literature on neuropsychiatric complications involving the central nervous system after spinal anesthesia and report six such cases which they observed. These complications may be in the nature of septic and aseptic meningitis, cranial nerve involvement (second, fourth, sixth, seventh, eighth, and twelfth), cauda equina neuritis with impaired bladder and rectal function, hemiplegia and paraplegia, pyramidal tract degeneration, meningoencephalitis, polioencephalitis, myelitis, myelopathies with adhesive arachnoiditis and radiculitis, and neuritis. Four of their six reported cases developed neurological symptoms immediately following spinal anesthesia.

One had signs and symptoms of a transverse myelitis, two of cauda equina neuritis and conus medullaris involvement and one of pyramidal tract involvement. All the cases showed little or no recovery after periods ranging from one to four years.

Kennedy and his co-workers<sup>81</sup> report three verified cases of spinal arachnoiditis and paralysis following spinal anesthesia. These patients who had developed adhesive arachnoiditis following spinal anesthesia were all explored and the adhesive arachnoiditis verified. The attempt was made to break up these adhesions. Two of the patients showed some improvement and the other remained unimproved, with paraplegia.

### Neurosyphilis

**Penicillin and Syphilis**—Not enough time has elapsed, and too few patients with neurosyphilis have been treated for a sufficiently long period of time, to make any definite statement concerning the results that might be anticipated. There is some evidence to suggest that the results in the treatment of neurosyphilis are not as striking as in early syphilis. Some cases of congenital syphilis have been treated in which good early results have been obtained. It is agreed by all who are investigating this problem that penicillin in the treatment of syphilis is still in the stage of preliminary investigation and no definite schedule of treatment can be recommended for routine treatment. During the treatment of syphilis with penicillin, Herxheimer reactions may occur. These are characterized by fever, malaise, and headache. These reactions subside usually within twenty-four to forty-eight hours and are not counterindications to continuing treatment.

Gammon and his co-workers<sup>82</sup> report their observations on blood and spinal

fluid of eighty-nine cases treated with penicillin. These patients were given sodium penicillin in aqueous solution intramuscularly for eight days, every three or four hours, for a total dose of 1.2 or 2.4 million Oxford units; a few received 3.0 or 4.0 million units. Penicillin improved the spinal fluid in all its elements and, to a lesser degree, the blood serology tests. The greatest effect was on the spinal fluid cells and protein; only six of the whole group failed to become normal in respect to these items. Of the various types of neurosyphilis, tabetic patients showed the least improvement in blood and spinal fluid. The fluids showing the greatest abnormality improved most. The character of the fluid rather than the clinical type of the case seemed to determine the response. Improvements apparently continued for as long as four months. Both dosage and length of treatment were important in the result. The better results were obtained from a high dose rather than a low one. The best results were obtained from a high dose given in two courses of retreatment, when the length of treatment was increased. The effect of time was important as well as dosage. The authors are now increasing their treatment dosage to 4.8 million units, which may be given in a single course of eight days and split into 2.4 million units administered in two courses at different times.

McDermott and Nelson<sup>83</sup> made a study of the transfer of penicillin into the cerebrospinal fluid following parenteral administration, using the dilution technic of bioassay. No penicillin was demonstrable in the cerebrospinal fluid obtain from seventy patients who had received penicillin in various dosages by parenteral routes. However, the authors have found improvement in the less acute forms of neurosyphilis without the de-



monstrable presence of penicillin in the cerebrospinal fluid. From their clinical studies they conclude that the concentration of penicillin which can be attained in the site of the infection in the central nervous system is sufficient to be effective in many patients with neurosyphilis and at least in some patients with purulent meningitis. Hence, intramuscular penicillin treatment is satisfactory in neurosyphilis and it is not necessary to use the intrathecal route for the treatment of these conditions. Neymann and his colleagues<sup>84</sup> investigated the method of administration of massive doses of penicillin in five patients afflicted with late syphilis of the central nervous system. In experimenting on subarachnoid administration, the direct intracisternal route was chosen. Single injections of 30,000 Oxford units appear to be tolerated without any untoward effects except occasional vomiting for a few hours. This dosage was administered daily to three patients for two weeks. The penicillin titers in the spinal fluid ranged between 0.7 and 11.6 units per cc., but no traces were found in the spinal fluid after thirty-six hours. Intramuscular injections of 350,000 units had no effect on the spinal fluid penicillin. Of the five patients with paresis reported in this investigation, only one improved clinically. This patient and one other, who remained demented, showed a change in serologic reaction, the latter becoming practically negative. Two patients lapsed into coma and died ten days after the last intracisternal injection. Another patient died as a result of exhaustion two weeks after treatment ceased. The blood Wassermann reaction of all five patients remained positive. They conclude that intravenous and intramuscular injections of penicillin for the treatment of dementia paralytica is not effective and that the intracisternal

route is dangerous if more than 30,000 units is injected and if the daily injections of this drug exceed five days. They are of the opinion that it is likely that chronic pachymeningitis and leptomeningitis are favorably influenced by the drug but the syphilitic involvement of the parenchyma in the depth of the cortex probably remains unchanged.

Rose,<sup>85</sup> in a study of 140 cases of symptomatic neurosyphilis, states that penicillin is an active therapeutic agent in all forms of neurosyphilis but that the degree of effectiveness has not been determined. The best results are obtained in syphilitic meningitis. A small series of cases of primary optic atrophy has shown surprisingly good results. All forms of parenchymatous neurosyphilis apparently need fever therapy as well as penicillin. The treatment he recommends consists of one half the usually prescribed amount of *fever therapy* and *penicillin*, given concurrently or in succession. Sodium penicillin dissolved in saline solution was administered intramuscularly for a total dose of 3,000,000 Oxford units. Goldman<sup>86</sup> reports on the treatment of eighteen cases of dementia paralytica and four patients with tabes dorsalis. Patients with dementia paralytica were divided into two groups, one of which was treated with a combination of intraspinal and intramuscular penicillin; the other with fever and intramuscular penicillin alone. With only two exceptions, marked clinical improvement occurred in both groups of patients. The author states that some of these are apparently recovering rapidly from their disease following treatment. In the first group, for six days the patients received intrathecal penicillin: On the first two days, 10,000 units each day and on the subsequent four days, 20,000 units each day. Twenty cc. of spinal fluid and penicillin solution were thor-

oroughly mixed. Then the mixed penicillin and spinal fluid were reinjected slowly, approximately twenty-five minutes taken for the injection. During the same period, the patient received intramuscular injections of penicillin into the gluteal muscles, 20,000 or 25,000 units being injected every four hours. A total of 900,000 units of penicillin, including the intraspinal injections, was given with the first course. A month after this, another series of intramuscular injections alone was given totaling 1,000,000 units. The second group of patients was treated with a combination of artificial fever and intramuscular injections of penicillin. A total of approximately thirty hours of fever by means of the diathermy induction current was given to each patient. This consisted of three sessions of two and one-half to three hours at 105° F. each week for a period of four weeks. After the third or fourth fever treatment, penicillin, 25,000 units every four hours to a total of 1,000,000 units, was given. After one month 1,000,000 units was injected in a similar manner with the fever treatment. Four patients with *tabes dorsalis* were treated by him with intrathecal penicillin alone. Two patients who suffered with tabetic crises showed improvement that was almost immediate. The method of administration was the same as that used for the parietic patients. Six daily injections were administered with a total of 100,000 units of penicillin. Stokes and his collaborators,<sup>87</sup> following their use of penicillin in the treatment of various forms of late neurosyphilis, state that sodium penicillin is an effective therapeutic agent in the treatment of late syphilis. Under conditions not yet clearly defined, it produces transformations symptomatically and serologically without reaction, or serious inconvenience to the patient, which are equal if not superior to those

obtained by long and arduous procedures involving the arsenicals and heavy metals. Moore<sup>88</sup> reports that in neurosyphilis little can be said as yet as regards the effectiveness of penicillin treatment. Some degree of immediate clinical improvement is apparent in most symptomatic cases; but whether these results are as frequent or as complete as after fever therapy is as yet debatable. He points out that there are four schedules under trial in the treatment of neurosyphilis. These are (1) repeated courses of relatively small doses, *e. g.*, 1,000,000 units, separated by rest intervals; (2) single massive dose courses, ranging from 2,000,000 to 6,000,000 units, given within eight to twenty or more days. In general, the larger doses are under study in patients with paresis, pre paresis, or primary optic atrophy; the smaller doses in less serious forms of neurosyphilis. (3) Malaria plus 2,000,000 to 4,000,000 units of penicillin simultaneously administered, an expedient possible because of the lack of effect of penicillin on malaria. There is some indication that penicillin, like other drugs, is more effective at fever than at normal body temperatures. (4) Malaria followed by penicillin. Nelson and Duncan<sup>89</sup> report that in ten cases of acute syphilitic meningitis treated with penicillin the immediate results (98 to 310 days after treatment) are excellent both from clinical and laboratory standpoints. Although penicillin does not appear in cerebrospinal fluid, even after frequent intramuscular administration, the drug is effective in acute syphilitic meningitis when given by the intramuscular route. None of the ten patients treated had developed any evidence of clinical relapse. The treatment schedule advised in this disease is a total dosage of 2,000,000 to 3,000,000 (Oxford units of penicillin). The drug is administered every three to four hours,

day and night, for from eight to sixteen days. There seems to be no reason to suggest intravenous or intrathecal administration.

**Other Therapies**—In neurosyphilis, Barnett and Meininger<sup>90</sup> found the use of *sobisminol mass* useful in the treatment of neurosyphilis. It is comparatively innocuous and its toxicity is low. About one third of the patients who took it experienced mild gastrointestinal disturbances. No serious reactions were encountered. Most patients tolerate the drug best when it is taken immediately after meals. The capsule should be followed by at least one glass of fluid. On rare occasions, soreness of the gums, a suspicious bismuth line, or a suggestive dermatitis have been observed. They are of the opinion that sobisminol mass is a valuable adjunct to antisyphilitic therapy. Results of treatment for shooting pains in tabes dorsalis have been unsatisfactory in the past. In 1942 Stone reported good results in tabes dorsalis from the use of intraspinal and oral *vitamin B<sub>1</sub>*. Kesert and Grossman<sup>91</sup> report eight cases of tabes dorsalis treated in this fashion. The optimum dose they administered intrathecally is 50 mg., but as high as 100 mg. may be given at one time. It was necessary to give some patients three or four intraspinal injections. They obtained relief with this regimen in patients suffering with gastric crises, as well as patients who suffered severe tabetic pains in the leg.

Smith and his collaborators<sup>92</sup> present the histories of nineteen patients with paresis who were treated with intravenous triple typhoid vaccine. The average number of fever bouts per individual was ten. Of the nineteen patients treated, sixteen were reported to have shown clinical improvement.

The term asymptomatic neurosyphilis is used to designate that group of patients with abnormalities in the cerebrospinal fluid due to the presence of the syphilitic virus in the central nervous system, though there are no clinical symptoms and no clinical signs of this involvement except the cerebrospinal fluid abnormality. Asymptomatic neurosyphilis is always the forerunner of symptomatic neurosyphilis in its disabling form, and for this reason the importance of recognizing neurosyphilis in the asymptomatic stage cannot be overemphasized. Merritt,<sup>93</sup> in a comprehensive review of asymptomatic syphilis, states that five or more years after initial infection with syphilis, asymptomatic syphilis was present in 9.5 per cent of 2263 patients with syphilis. After this there is a decrease in frequency of asymptomatic syphilis due to the development of symptomatic syphilis. Since the value of penicillin has not been established, Merritt confines his discussion to those methods of treatment whose value has been proven by extensive trial. These include (1) routine treatment with trivalent *arsenicals* and *bismuth*, (2) *tryparsamide*, and (3) *fever therapy*. In patients who have received thirty or more injections of trivalent arsenicals and in whom the cerebrospinal fluid is markedly abnormal, the treatment should be changed to tryparsamide or fever therapy. Hobhouse<sup>94</sup> records a case of syphilitic wrist drop in a woman forty-four years of age. She developed bilateral wrist drop. The clinical picture was that of a polyneuritis. Blood and spinal fluid serology were both positive. Under treatment with iodides, bismuth, and mercury, the patient experienced improvement. The writer suggests that examination of the spinal fluid is indicated in cases of neuritis whose course is more gradual than that of infectious

polyneuritis. Arieti<sup>95</sup> gives an account of his review of the literature of paresis in senility and reports on six cases which he studied clinicopathologically. General paresis occurs in senility with considerable frequency. In the state of New York, about 10 per cent of paretics admitted for the first time to a state hospital are sixty years old or more. The incubation of the senile type of paresis is generally extremely long (forty to fifty years) or rather short (five to seven years). The diagnosis is often made difficult by the fact that the blood serology is negative in spite of the progress of the histologic inflammatory process. Pathological studies revealed that these cases may be divided into two groups: First group, by far the least common, characterized by intense inflammatory changes, presence of alterations typical of senility, and absence of arteriosclerotic lesions; the second group, characterized by milder inflammatory changes, absence of alterations typical of senility, and the almost constant presence of arteriosclerotic lesions. The author feels that neurosyphilis may accelerate the arteriosclerotic process in the brain.

### Poliomyelitis

**Epidemiology**—Sabin and Ward, in their study of human poliomyelitis, demonstrated that the human alimentary tract, from mouth and pharynx to the colon, may be a port of entry for the virus to the body and particularly to the central nervous system. This work has been confirmed. The virus has been found in human stools, in sewage, and it has been reported by White and Dougherty<sup>96</sup> in flies. These results have led to renewed studies of the transmission of the virus by flies from human stool or sewage to a noninfected person. Ward and his co-workers<sup>97</sup> report direct evidence that fecal material, sewage, or

contact with flies by the individual, his food or fomites may actually constitute a link in the chain of the infection with poliomyelitis. Horstmann and his colleagues<sup>98</sup> made a study of the persistence of virus excreted in the stools of poliomyelitic patients. The results of their study indicate that the period of virus excretion is longer than a month after the infection is acquired and may extend into the third and eighth weeks in an appreciable percentage of cases. Not one of the sixty-one patients followed was demonstrated to become a persistent carrier of poliomyelitis virus. Sixty-one per cent of these patients excreted virus during the first two weeks after the onset of the disease, 50 per cent during the third and fourth weeks, 27 per cent at the fifth and sixth weeks, 12.5 per cent at the seventh and eighth weeks. Howe and his collaborators<sup>99</sup> report their observations on the presence of poliomyelitis virus in the human oropharynx. Poliomyelitis virus was demonstrated in pharyngeal swabs taken from patients with the disease of the spinal and bulbar paralytic, and non-paralytic type as well. Virus was found to be present in 43 per cent of a series of twenty-three cases from whom swabs were taken during the first three days of illness. In no instance was virus found after the third day of illness (thirteen cases). Seddon and his colleagues<sup>100,101</sup> report their experiences with the poliomyelitis epidemic in Malta. The outbreak included 483 paralytic cases. The epidemic developed rapidly at a time when flies were less numerous than at other seasons. They noted that the pattern of the epidemic corresponded to that of a respiratory type of infection. The authors suggest that the virus may be constantly with us, constantly infecting us, but only rarely getting through to infect the central nervous system.

About three years ago, Foster and his associates reported that the resistance of mice to poliomyelitis virus was increased as a result of thiamine deficiency and that a similar less pronounced increase in antiviral resistance resulted in other forms of malnutrition. Clarke and his associates<sup>102</sup> have attempted to confirm the seemingly paradoxical results on monkeys. They conclude from their findings that in contrast to the well-confirmed increase in antiviral resistance in thiamine deficient mice, vitamin deficiency does not materially alter poliomyelitis susceptibility in monkeys.

**Pathology**—Bodian and Howe<sup>103</sup> report on their studies of experimental nonparalytic poliomyelitis. A series of thirty-seven monkeys inoculated intracerebrally with material from throat swabs of poliomyelitic patients was examined histopathologically to make certain that nonparalytic poliomyelitis was not missed, as well as to confirm the clinical diagnosis of poliomyelitis in the paralytic monkeys. Ten of the thirty-seven monkeys suffered attacks of poliomyelitis. Of these, nine were paralyzed and one had a nonparalytic infection. The pathological findings in all cases were typical of poliomyelitis. The occurrence of one nonparalytic infection in a total of ten monkeys inoculated intracerebrally is to be compared with a similar frequency of nonparalytic infections in monkeys inoculated intranasally with human and chimpanzee stools (human stools, forty-five paralytic and five nonparalytic; chimpanzee stools, forty-three paralytic and seven nonparalytic). Sixteen showed scattered perivascular infiltrations in the pia mater, which were interpreted as nonspecific reactions to the inoculation. Saphir<sup>104</sup> made an extensive study of the visceral lesions in poliomyelitis. The findings at necropsy on seventeen patients dying

from poliomyelitis were studied. The changes in the brain and spinal cord were not unusual. In ten instances, myocarditis was found. The pathologic changes were detected only on microscopic examination and varied greatly in extent and severity. Often it was noted in the vicinity of minute or larger epicardial or endocardial petechial hemorrhages. The sudden death of some of these patients may be attributed to the myocarditis. Interstitial pneumonia was encountered six times. There is a possibility that the pulmonary lesions were caused by a virus. Bronchopneumonia was present five times.

**Treatment**—A recent study by Watkins and Brazier<sup>105</sup> was concerned with the effect of various forms of thermal therapy and of neostigmine on muscle spasm as recorded by the standardized electromyographic method. These investigators studied the effect of a single application of a therapeutic agent on muscle spasm during the first weeks of the disease. The methods investigated were twenty net applications of the Kenny type of *hot packs, infrared irradiation, luminous heat, short wave diathermy* by induction technic, and intramuscular injections of 1.6 mg. of *neostigmine methyl sulfate*. They found that single application of hot packs, infrared irradiation, and diathermy were without effect on the muscle spasm. Luminous heat and neostigmine caused a decrease in spasms of approximately 25 per cent. This degree of change was not great enough to indicate a specific effect on spasm. These authors observed, moreover, the effect of only a single application and not the effect of repeated injections of neostigmine as used by Kabat (see 1945 SERVICE VOLUME). Brainerd and his collaborators<sup>106</sup> discuss the clinical manifestations of poliomyelitis with special attention to the treatment of this condi-

tion with neostigmine and the Kenny method. They found that muscle spasm was of uniform occurrence in early poliomyelitis and was of great diagnostic value. The spasm did not appear to be due primarily to meningeal irritation. Spinal fluid pleocytosis was frequently absent. Neostigmine methyl sulfate was found to relax the muscle spasm of poliomyelitis at least temporarily. They conclude that the value of continued medication with neostigmine, oral or subcutaneously, requires further proof, but its continued trial under controlled circumstances is definitely warranted. They found that the Kenny treatment with or without neostigmine was an effective method of preventing contractures and deformities. Their study gave no proof or disproof that either neostigmine or Kenny pack reduced the incidence of paralysis. In the patients that were treated with neostigmine, this drug was administered subcutaneously every other day in similar doses to that used in the one-hour test which is initially tried to determine the ability of the drug to relax muscle spasm and increase motor power. In addition, most patients also received *neostigmine bromide* by mouth thrice daily. Children under six years received 0.5 mg.; those of six to twelve years, 1.0 mg.; and adults 1.5 mg. accompanied by 0.4 mg. and 0.6 mg. of *atropine* in the latter two age groups. Children under six years received 15 mg. orally three times daily; those from six to twelve years received 30 mg. thrice daily, and adults received 45 mg. on a similar schedule. When side effects such as nausea, diarrhea, or urgency occurred, increased atropinization almost always gave relief. No serious toxic effects of neostigmine were noted.

Fox and Spankus<sup>107</sup> also evaluate the use of neostigmine in acute anterior poliomyelitis. Two methods of adminis-

tration were used in their study: (1) Thirteen of the patients received single daily subcutaneous injections of 1:2000 neostigmine, the usual dose being 1.0 mg.; (2) six of these patients were changed to oral administration after four to thirteen days, and eleven additional patients received the oral neostigmine from the beginning of their therapy. The orally administered neostigmine was given twice daily, 30 mg. being given at 8 A. M. with 15 mg. at 6 P. M. *Atropine sulfate* was administered hypodermically to control parasympathetic reactions. The degree of daily relaxation of the involved muscles produced by neostigmine was determined by measuring increases in passive motion which are present seven hours after the administration of the drug. Results for each patient were compared from day to day. The total amount of relaxation obtained in the spastic muscles during the patient's entire therapeutic period was also determined and results were compared with a control group of six patients who did not receive the neostigmine. Both groups of patients had been given hot fomentation treatments according to the Kenny technic. In these cases of acute poliomyelitis, the neostigmine caused a partial relaxation of spastic muscles which was neither pronounced nor constant and which was characterized by irregularity. Nevertheless, it was concluded that the combined use of neostigmine with hot fomentations resulted in a persistent and perceptible relaxation of spastic muscles in most of the cases of acute anterior poliomyelitis. These observations were limited to the acute phase of poliomyelitis and not to the effect of neostigmine on the subacute or chronic phase of the disease. Neostigmine was of little value in cases of bulbar poliomyelitis in which it was tried. The special committee headed by McIntosh, which was appointed by the

Scientific Advisory Board of the National Foundation for Infantile Paralysis, emphasizes that of the various forms of treatment it is of the utmost importance to determine the procedure to be recommended when an epidemic strikes. The committee<sup>108</sup> has indicated a program which might be undertaken to determine uniform methods of evaluation.

Sherman<sup>109</sup> presents a final report on seventy cases of acute anterior poliomyelitis which were treated in 1943 by only general supportive therapy. The survey revealed that 10 per cent had enough residual weakness to require braces or further surgery, 72.8 per cent had no residual weakness or such slight weakness that it was barely detectible, and 8.6 per cent had functional significant weakness which did not require further therapy and which did not constitute a handicap to normal life. No patient has regressed. Major improvements have occurred without exception in those patients who had not been completely paralyzed. The author states that the latter course of these patients supports further the recently ignored fact that the amount of ultimate recovery depends primarily on the extent of the initial involvement of the central nervous system and not on the type of treatment.

Nelson-Jones and Williams<sup>110</sup> point out that laryngeal obstruction is a possible cause of dyspnea, anoxia, and death in bulbar poliomyelitis. It may occur from adduction of the vocal cords, or from filling of the larynx with saliva and secretions of the nose and throat which cannot be swallowed owing to paralysis of pharynx and esophagus, or from both these causes. The treatment suggested includes tracheotomy, which should not be left until the patient is *in extremis*; aspiration by rubber catheter passed from time to time into the tracheotomy tube connected with electric suction; penicillin

and sulfathiazole during first week; vocal rest, and a nutritious fluid diet with adequate vitamin content given by Ryle tube, which can be tolerated for weeks with occasional removal for cleansing. Hilbish<sup>111</sup> reports a case in which a gastrostomy was performed for prolonged inability to swallow in a case of bulbar poliomyelitis. This proved a life-saving measure in the case reported. When first seen, the patient had a severe bulbar poliomyelitis and it was impossible to tube feed her because of an obstruction which seemed present in the lower end of the esophagus. It was difficult to continue intravenous feeding because the patient was in a respirator. The gastrostomy was performed under local anesthesia without difficulty. The gastrostomy tube was left *in situ* until the patient had recovered sufficiently to take food by mouth.

Wyllie<sup>112</sup> presents a report of a patient with a second attack of poliomyelitis after thirteen years. The first attack had left the patient with a wasting and flabbiness of the calf muscles of the right leg but with little loss of function. During the second attack, she had a partial paralysis of both legs with weakness of the lumbar muscles. Fox and Sennett<sup>113</sup> give an account of the clinical course of four women with poliomyelitis who were pregnant. Two of the women delivered normal children and examination of one fetus in a dead mother confirmed the opinion that poliomyelitis in the mother had not affected the newborn child nor did it prevent normal spontaneous delivery. Blair and Robertson<sup>114</sup> present their experience with pregnancy in the presence of maternal poliomyelitis. Six cases were observed in this series. All had normal children. The safety of the child *in utero*, even in the presence of the most virulent attack compatible with life, is well dem-

onstrated in this series. Those infants that were born were well and showed no clinical manifestations of infection.

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## PSYCHIATRY

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## WAR VETERANS AND THEIR FAMILIES

KENNETH E. APPEL, M.D.

EDITOR'S NOTE—*All doctors will be consulted about problems arising in the families of returning service men. The following account of how best to help these men psychologically is taken from the recent book "Psychiatry in Modern Warfare."*

### Every Soldier Has a Readjustment Problem<sup>1</sup>

There are four groups of men that have to be considered: The 4 Fs; those discharged for neuropsychiatric reasons or because they were unadaptable to military service; the wounded and maimed; and the men who have carried on through terrific strains and experiences, who have escaped injury, and who have survived with physical and mental health.

The return to civilian life demands a change in attitude, orientation, and behavior. Military life itself is a strain and a source of tension. With the cessation of hostilities, all the habits, stimulations, and emotional mobilizations incident to army life are supposed suddenly to cease, be given up and changed. This is almost impossible because habits, memories, and emotions do not cease either physiologically or psychologically at the giving of a command or blowing of a bugle. Time is required for readjustment and change. Reactions to these changes vary all the way from apathy and indifference, guilt and depression, fear and uncommon sensitivity to noises, to restlessness, impatience, irritability, pugnacity, and erratic or extreme conduct.

Other factors, in addition to the ones mentioned, must be recognized in order to understand and help the returning soldiers. They have old frustrations, disappointments, and uncertainties, remaining from the time they left civilian life. These are latent or repressed sources of irritation, apprehension, and confusion which will be lighted up again. Many have had to interrupt their education and surrender their ambitions. Many more have had to give up jobs which gave them security, economic competence, interest, and opportunity to pursue their life goals. Their individuality has been submerged. They have been completely dependent on the orders, organization, and provision of others. With the cessation of war, they are asked, required, to change all this, and this is often impossible in even the best-adjusted, healthy soldier. Civilians are expecting the impossible. Besides all this, the veterans are suddenly immersed in new types of relationships at home, with wives and children, parents and sweethearts. Naturally, there is trouble in formulating plans, making decisions, being cooperative, showing resourcefulness and initiative, and in executing plans doggedly and consistently.

### The Philosophy of Helping

Four considerations should be borne in mind by all those helping the soldier readjust to civilian life:

1. The majority of men returning from military service, in spite of difficulties, will be able to achieve the military-

civilian change and adjustment to home, job, and community by themselves. Only a relatively small number, considering the total involved, will need psychotherapy.

2. The specific acute reactions will be transitory, will improve, and will disappear in the majority of men in several months.

3. Ultimately, the successful adjustment of the veteran will depend on that quality of his prewar personality which we call morale or maturity—actually on his own determination to succeed and persist through difficulties, disappointments, trials, and error.

4. The burden of readjustment must not be placed alone on the ex-service man. Readjustment is a cooperative process. Civilians must readjust, too! They must develop new perspectives and attitudes. They will have new responsibilities which they must assume, of changing, of recognizing important factors involved in all human relationships, and they themselves must make the proper efforts to help.

Perhaps there are four main factors which determine the size and shape of each adjustment problem:

1. The personality of the man before he entered the military service.

2. The effect upon the personality of the military experience.

3. The environmental setting (personal, social, and occupational) from which the soldier was removed in order to serve his country.

4. The changed personal, social, and occupational situation to which the soldier returns and to which he is asked to adjust.

The largest single dischargee diagnosis from the armed services has been "psychoneurosis." The incidence has been startlingly high, relatively much higher than in World War I. We do

not believe that by any means all of this high incidence represents the clinical psychoneuroses of civilian psychiatry. Many are vaguely defined psychoneurotic reactions, often with somewhat vague psychosomatic complaints; many represent chronic psychopathic behavior; many more express "military inadaptability," *i. e.*, an inability of the personality to adjust to the necessary regimentation and discipline of military life. It is not unlikely that many in this latter group will readjust to civilian life without too much friction. One may be reasonably hopeful, too, concerning the adjustment of a considerable number of authentic psychoneuroses. Several reports from industry would seem to indicate that psychoneurotic dischargees have a better work record than civilian workers who have not been in the Army. Perhaps in the contribution to this good record there is included the motivation of a sincere desire to justify to self and others the failure to continue in the military service.

There is one reaction to the adjustment problem which is extremely common. In the far-flung outposts of war, the one bright sustaining thought has been of "home" and its joys and it is not unnatural that these included a certain amount of overidealization. When the soldier returns, at first everything is wonderful—then time begins to drag—somewhat to his surprise, he begins to miss the old "outfit" and the feeling of orientation and security he felt in the army even when "the going was rough." Now, in a condition compounded of disillusionment and insecurity about the future according to his particular personality, he begins to react with one of the many degrees of overreaction or underreaction. He may be genuinely frightened and act timid, shy, or self-conscious, or he may childishly retire to

his tent because of disappointment, self-pity, and insecurity, and sulk. Or, rather, more likely there will be a display of aggressiveness, varying from irritability to outright pugnacity. There may be the insistent and emphatic demand for special privileges. There may be exhibitionistic displays of profanity and obscenity, sometimes seemingly increasing apace in proportion to the manifestations shown by family and friends of being shocked.

The measuring rod of maturity is what we must use to determine the degree of adjustment which can be obtained. The maturity of both the returnee and those to whom he returns. Maturity in this connection is a quality of personality that is made of a number of elements—it is the ability to stick to a job until it is finished. It is the capacity of giving more than is required in a given situation. It is reliability. It is the ability to endure unpleasantness, frustration, hardship—to make one's own decisions. It implies independence, determination, and a will to live. It represents the capacity to work with others and under authority. If the returnee is reasonably mature, he will be responsive to mature efforts to help him. There may be many complicated problems but they will be solved if there is enough maturity available to be mobilized into effective conduct.

Returnees who have served in unusual branches of the service, rendering service in media that are in some sense both unphysiological and unpsychological (like the flying personnel of the air forces, those in submarines, the paratroopers, and the commandos), often will constitute difficult and special problems of adjustment, emotional, social, and occupational. It will not be a simple matter for these men to settle down to everyday living: the routine commonplaces of family and social life with

perhaps a humble clerkship in some huge hive of industry. All of them have had the adulation given to heroes. Above all else, time and patient forbearance is needed in helping them adjust to the tempo of a peaceful civilization.

### Methods of Helping Returning Service Men

Admittedly, the absorbing of millions of returned soldiers into industry and finding satisfactory work for those who are willing and either able to do it or trainable is an undertaking of the first magnitude.

Irrespective of economic opportunity, the employer must exercise a reasonable amount of patience and assist the returnee in adjusting to his job. There will be a number of hurdles for the returnee and the employer to take together. The returnee is apt to resent the timeclock, particularly in view of the fact that the abrupt transition back to civilian life has produced a temporary phase of restlessness. In the Army there was much discussion about the high wages paid to the war industry workers and the returnee may feel he is being inadequately paid. He may feel, too, that he should have special consideration because he has risked his life for his country. If his personality contains a segment of suspiciousness, he may readily develop the belief that he is being discriminated against. However, if the veteran is reasonably mature and the employer is patient and considerate, it will not take overlong for the wheat to be separated from the chaff. The chaff will consist largely of the real psychopath who is chronically maladjusted and whose failure to adjust to employment is merely another episode in a lifelong history of inadequacy, emotional, social, and occupational.

Naturally, the employer is concerned about the discharge diagnosis of the returned soldier, particularly if the diagnosis is a neuropsychiatric one. He is somewhat too ready to believe that it constitutes *prima facie* evidence of a bad employment risk. Here is a challenge to psychiatrists in the armed services, in the Public Health Service, and in the Veterans' Administration; to civilian psychiatrists, and to other sources of valid information. A program of education for the employer is already under way, but even greater effort is needed. It cannot be reiterated too often that the vast majority of military neuropsychiatric diagnoses do not signify an incapacity to become an effective worker.

What are the attitudes that family, employer, and community can adopt that will help the men returning from war? They are the attitudes that afford constructive help to people generally and which do not block and discourage people. One should bear in mind the needs of people; the need of individuality, to be one's self, to feel that one counts for something, and deserves some respect and consideration, even if one is not well or is not temporarily succeeding in making a go of life socially or economically. There are needs for a certain amount of freedom, independence, and self-direction, with the freedom to explore, try, make mistakes, and learn from them.

To serve these needs of the returned service men, those who are trying to help will be warm, kindly, and supporting; will be considerate, accepting, sympathetic but not indulgent; will show interest in the soldier's concerns and problems, and occasionally offer suggestions of possible and alternate plans of action. They will leave the man free to select and decide for himself. It takes time to grow, to make adjustments. Therefore, patience

is necessary and not hastiness. Sympathy not indulgence; kindness and consideration, not domination; tolerance not criticism are required.

The public needs a great deal of education in regard to the diagnosis of psychoneurosis. "Psycho" does not mean insane. There is relatively little insanity in the armed forces. The man with psychoneurosis is less dangerous than the average man in the population. Having been psychoneurotic in the army does not mean he will be psychoneurotic in civilian life. Psychoneurotic essentially means that the individual is overstimulated, that he is filled with tensions which manifest themselves physiologically and psychologically, that he is overreactive and emotional.

The physician who treats the psychoneurotic veteran will "not rely upon stock cures." He will not "overemphasize any one pet theory or method of treatment to the exclusion of a careful study of the whole person and his illness. He knows that the 'rest cure' has its place when indicated," but he will not rely on this alone. He will not rely on diversion, trips, and vacations. He will "not overuse work, rest, exercise, occupation, massage, electrotherapy, hydrotherapy, recreation, or any one thing" but will use "each with discrimination as indicated." And, above all, he will "not dispense platitudes, indiscriminate encouragement, slaps on the back, bawlings out, pep talks, scoldings, descriptive names or accusations of cowardice, stupidity, malingering, or laziness. He knows that it does not suffice to have the psychoneurotic return to the office occasionally for a quick check-up. He will settle for nothing less than an intelligent, sound, careful understanding of the real psychopathological condition, its causes and dynamics, and a

psychotherapy and medical therapy based upon the removal and modification of the causes, comprehensive reeducation, and a constructive building of real health in mind and body." And this is possible with patience and time.

There will be inevitably a "fantastic" manpower shortage in physicians equipped to care for psychiatric conditions. This represents a challenge to our communities, to manpower commissions, to psychiatrists, to politicians, to physicians, and to medical education. As has been said, we have fallen down in psychiatric education. The newer developments in group therapy will be a help. But we need more physicians trained in psychiatry, more clinics, more community facilities for dealing with this problem. There will be a need for more civic centers for both recreational and educational activities. We should build veterans' hospitals in the center of large

communities, close to our best hospitals and medical schools.

Our schools, colleges, and universities must share part of the responsibility not only for the development of these conditions but for inadequate facilities. The churches, and the home, and our mores in general must share the blame. Morale and maturity as we have defined them must be a part of real education for life. Lectures and group discussions should be undertaken. There is need for increased awareness and publicization of the facts. Let us keep the same spirit of enterprise, resourcefulness, and achievement which we used during the war, energized for the challenging problems of the returned service men and the responsibilities of peace.

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## WAR NEUROSES

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War neuroses occur not only in individuals predisposed by previous emotional disorder or personality defect, but also in those who had been psychologically strong. This has been shown clearly in Grinker and Spiegel's recent book,<sup>1</sup> in which they relate their observations on psychiatric casualties among fliers. A previous publication<sup>2</sup> dealt with battle casualties among ground force personnel during the North African Campaign.

These authors distinguish between fliers showing symptoms after minimal stress and those in whom symptoms appear only after severe stress. The first group is composed of those men who were predisposed to psychiatric disorders and thus were unsuited to combat flying. This group they separate

into three classes: (1) Those who have conflict between their underlying insecurity and their sense of duty. These men show neurotic symptoms of all kinds. (2) Men with little sense of duty, but who show early anxiety because of their underlying insecurity. (3) Those fliers who previously have been unable to adjust to groups or yield to authority and who, under minimal combat stress, show behavior difficulties.

Fliers who break down only under severe stress do so more because of the pressure of external events, rather than because of any predisposing internal weakness. In these men every type of psychological and psychosomatic symptom may be seen. There is considerable overlapping of the clinical pictures, but they tend to fall into five categories:

(1) Free anxiety states; (2) phobic states; (3) conversion states; (4) psychosomatic reactions, and (5) depressions.

Grinker and Spiegel also discuss the psychiatric states seen in men returned to this country from combat areas. Returnees sent to an Air Forces convalescent hospital included not only fliers who had psychiatric help overseas, but many who develop crippling symptoms for the first time on their return home. The authors divide these returnee patients into the following groups:

(1) Passive-dependent states; (2) psychosomatic states; (3) guilt and depression; (4) aggressive and hostile reactions; (5) psychotic-like states.

### Narcosynthesis in the Treatment of War Neuroses

The need for shortened forms of psychotherapy was quite apparent during the recent war, when it was necessary to treat and quickly return to duty large numbers of psychiatric casualties. Both hypnosis and hypnotic drugs have been used to aid in the recovery of repressed material. Fisher (1943) reported on the use of hypnosis in the treatment of war neuroses, while Grinker and Spiegel<sup>1,2</sup> made extensive use of *sodium pentothal*.

In civilian psychiatry before the war, intravenous *sodium amytal* was frequently used for "interviews" as a means of aiding the recovery of forgotten memories and as an aid to the therapist in more quickly gaining an understanding of the dynamics involved in the patient's neurosis. This procedure is sometimes labeled narcoanalysis.

The greatest gain in the use of intravenous barbiturates in therapy is their use to not only release repressed material, but also to aid in the resynthesis of

this dissociated material.<sup>3</sup> Grinker calls this technic narcosynthesis.

*Sodium pentothal*, in 2.5 or 5 per cent solution, is injected into the antecubital vein at a slow rate (0.1 gm. per minute) while the patient is asked to count. The injection is discontinued when the counting becomes confused and before actual sleep is produced. Many patients will begin to talk spontaneously, but others must be stimulated to talk by direct questions or preferably by describing to the patient what is known of the particular battle situation which is under investigation. Most men will then begin to quite freely relate an account of their part in the battle.

The use of *pentothal* should not be resorted to until the therapist is well acquainted with the patient. The drug may then be used to overcome resistances and hasten the process of resynthesizing the repressed material. Grinker and Spiegel are careful to point out that abreaction alone, under the influence of the drug, is rarely curative, but that subsequent interpretations and "working through" are necessary.

In some combat areas, prolonged narcosis therapy was used with reported good results. It was successful in many cases in England following the battle of Dunkirk. Hastings, Wright, and Glueck<sup>4</sup> made extensive use of it for patients in the Eighth Air Force. Grinker and Spiegel,<sup>1</sup> however, state that narcosis therapy was of no value in their patients in the Mediterranean area. It is not clear as to why there was this difference in results, but it should be remembered that sleep must be maintained at a deep level if disturbing nightmares are to be avoided. Furthermore, during the semiawakened periods when the patient is fed, a great deal of anxiety may be mobilized.<sup>1</sup> Much of the danger of this

may be avoided, however, if this period is used by the therapist for psychotherapy.

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## MENTAL DEFICIENCY

E. ARTHUR WHITNEY, M.D.

Lawrence<sup>1</sup> presents a case report on the Lawrence-Moon-Biedl syndrome. This condition was first described as "retinitis pigmentosa" by Lawrence and Moon over ninety years ago in a report of four cases with retinal defect plus the familial mental deficiency, obesity, hypogenitalism, and small stature. His cases are in an old Yankee family.

The mother was obese and short of stature. Her first-born child was obese, had six fingers on each hand and six toes on each foot and was unable to walk or talk at the age of three, when she died.

The second and third children were normal. The third, a stillborn male, was said to have had no abnormalities. The seventh was a very obese baby.

The fourth child (Case 1) is a female, aged  $8\frac{3}{4}$  years, walked at  $2\frac{1}{2}$  years, talked still later, and her speech is still limited and indistinct. Her height is  $51\frac{1}{2}$  inches; weight, 182 pounds. Genitalia, normal. Ophthalmic examination showed marked attenuation of retinal vessels, yellowish irregular patches; media and disks normal.

The fifth child (Case 2) is a female aged seven years, with a height of 44 inches, and a weight of 70 pounds. Her eyes showed persistent nystagmus with quick component to left. Vessels of retina were definitely attenuated.

The grandfather of these children may be the father of some of them, which would account for consanguinity frequently reported in this syndrome. There are several theories as to its possible causation.

1. A pituitary factor in both obesity and eye symptoms.

2. A familial form of dystrophy adiposogenitalis of cerebral rather than pituitary type.

3. A developmental defect of the ectopic zone.

4. An interplay of three genetic factors: One responsible for obesity, genital dystrophy, and dwarfism; one for retinitis pigmentosa, and one for the anomalies of polydactylism.

5. A form of internal hydrocephalus pressing on the infundibular stalk.

6. A result of two recessive genes in the same chromosome.

7. That it is not a syndrome at all, but merely a rare combination of more or less frequent "heredofamilial" anomalies.

Duffy<sup>2</sup> reviews the history and etiology of tuberous sclerosis, a condition also known as "Pringle's disease," epicola, and adenoma sebaceum. The cardinal symptoms of the condition, mental deficiency, epilepsy, and adenoma sebaceum, develop in early childhood or in infancy and are progressive. The cuta-



neous lesion usually develops within the first ten or twelve years. The course of the disease is fairly rapid, death being due to cachexia, pulmonary infiltration, or status epilepticus. Psychosis of the primitive schizophrenic catatonic type may develop.

The basic characteristics of tuberous sclerosis are developmental anomalies in tissues of ectodermal origin, particularly the brain, skin, and retina, but tumor formation may be noted in heart, kidneys, liver, thyroid, pancreas, ovary, and even lungs. Such stigmata of degeneration as harelip, spina bifida, polydactylism, and microcephaly may also be present. Three distinct types have been noted:

1. Pringle's type with lesions red in color which show microscopically an abundance of vascular and telangiectatic elements.

2. Belzare's type characterized by an absence of vascular elements.

3. Hallopean-Laredale type characterized by hard, firm nodules showing histologically excessive fibrosis.

The rhesus gene and its relationship to the etiology of obscure cases of mental deficiency are receiving more and more attention. Cook<sup>3</sup> presents a review of the subject and it is suggested by Yannett and Lieberman to be the possible cause of as much as 25 or 30 per cent of hitherto undifferentiated cases of mental retardation.

Canmann,<sup>4</sup> in a review of the literature of Niemann-Pick disease, finds fifty-nine cases reported since 1914, chiefly in Hebrew families. All cases died before the age of three. It is probably a congenital disease which affects both sexes equally and is characterized by retarded development, enlargement of liver, spleen, and lymph nodes, edema with or without ascites, brownish-yellow pigmenta-

tion of the skin, mongoloid appearance, and general emaciation.

Hurst<sup>5</sup> presents eleven case histories to illustrate the hereditary factors in mental disease and mental defect. He states that the weight of evidence is that intelligence in general is inherited in a multifactor manner, as in height and weight; and the bulk of the feeble-minded group constitute the lower end of the normal curve of distribution of intelligence. In the hereditary forms of mental defect, eugenics has great and valid scope, and sterilization can lay a more serious claim to consideration here than in cases of schizophrenia and epilepsy.

Glass<sup>6</sup> points out that in recent years irradiation of the pelvis of a pregnant woman may endanger fetal development. He reports a case of "radiogenic" microcephalic idiocy with dwarfism and renal rickets, in which the child died of septic meningitis. Significant findings at the autopsy showed: Dwarfism, hypoplasia of genitalia, breasts, and brain; pyelonephritis with renal rickets; adenomatous hyperplasia of one parathyroid gland; atrophy of bone marrow with fibrosis; irregular ossification of cartilaginous bones.

Familial microcephalic pedigrees are recorded by Halperin.<sup>7</sup> In one family, the last three sisters in a series of nine pregnancies were microcephalic. The mother's age at their births was twenty-nine, thirty-two, and thirty-four years. There was no history of syphilis, x-ray irradiation, or abnormalities of the pregnancies and subsequent labors. There was no history of consanguinity. Parents and other siblings were not affected.

Another family history was one of thirteen children with one stillborn. Of these, two were microcephalic. Here again there was no history of consanguinity, syphilis, irradiation, or abnor-

malities of the labor. He concludes that microcephaly is still an unsolved problem genetically.

Fincher<sup>8</sup> presents a pathological report on the findings in twenty operations in microcephalic skulls. In every one of the cases when the dura was opened either a green or a purple-tinged membrane was found in direct contact with the inner surface of the dura. This membrane, varying in thickness, could be separated from the dura without bleeding. The pia was often found under this membrane. Microscopically, the characteristics of this subdural membrane were not unlike pachymeningitis hemorrhagica.

The operative results obtained were: A diminution of Jacksonian seizure, where present, but no effect on intelligence. Some evidence of birth trauma found at operation might indicate that this is a factor in the production of the condition.

Follow-up studies on mental defectives have been either lacking or ineffectual. Muench,<sup>9</sup> however, presents an interesting study of eight cases followed up after a lapse of eighteen years. There were eight out of forty cases tested in 1925 and the retest was conducted in 1943. The results showed the following:

1. All showed an increase on the 1916 Binet scale resulting in a mean increase of 15.4 in I.Q. and 3.6 in M.A.
2. On Army Alpha Test, mean increases of 10.8 points.
3. On Porteus Maze Test, mean increases of 24 points.
4. On Ohio Literacy Test, increases were insignificant.
5. Seven of the eight are married.
6. Four of the married have total of 12 children.
7. None had a criminal record of serious offense.
8. Average salary, \$35.00 a week.

The author contends that there is little change possible in I.Q. under institutional care and where changes do occur they are apt to be losses rather than gains. He believes that the socially adjustable defective should be given an opportunity to try his wings in community life.

Hockett's<sup>10</sup> three-year review of progress in the field of mental retardation leads him to conclude that there are serious problems arising from the failure of secondary schools to recognize and meet the challenge of the backward child and that it is evident that there is a special need of dull pupils for vocational guidance. They should be led to choose unskilled or semiskilled work.

Daily (1943) believes that in special classes, special schools, and institutions the emphasis for adequate development of retarded children should be on activity. Participation in a varied program of folk dancing, group games, nature study, group swimming, excursion clubs, dramatic societies, group parties, motion pictures, and, in fact, any and all forms of cooperative activity. Such a program enables the retarded child to make normal contacts and normal friendships.

Hyde and Kingsley<sup>11</sup> have made exhaustive studies in the medical sociological aspects of mental rejections in 60,000 selectees examined at the Boston Armed Forces Induction Station. The rate of mental deficiency varied from 0.9 per cent in the better social communities or strata to 6.9 per cent in the poorest communities. The rate of psychopathic personality varied from 2.4 to 6.9 per cent. Rates tend to increase rapidly with a decline in the socioeconomic level with variations from the average being most noticeable at the two extremes of the community level. The highest rate of mental deficiency occurs in the semi-

rural areas and the lowest rates are found in the small cities.

Pollock<sup>12</sup> presents the vital subject of the incidence of mental disease among mental defectives. He gives an analysis of 444 mentally defective patients admitted to the state hospitals for the insane in New York in one year (1942). According to him, there is little to support the contention that mental disease is more prevalent among mental defectives than nondefectives.

Preventive medicine's most effective weapon in combating the rising incidence of hereditary types of mental deficiency is selective sterilization. Butler<sup>13</sup> states that, in California, of the 4310 cases committed and sterilized there were seven deaths, none of which could be traced to the operation itself. It is his opinion that it does not tend to increase promiscuity, venereal disease, and sex delinquency. He recommends for the furtherance of sterilization extramural laws permitting legal sterilization of bona fide cases by private surgeons, in private or general hospitals, the same as other surgery.

It is Conrad's<sup>14</sup> belief that education should be carried on for longer periods for the retarded in order that they may attain the maximum of their own potentialities. There seems to be a small but true relationship between intelligence and physical maturity. More studies are required to determine the possible influence of socioeconomic and racial factors.

Psychopathological studies on 302 children between the ages of six and sixteen at Santiago, Chile, are reported by Brucher (1943).

Nowrey<sup>15</sup> has presented a most complete history of the care and treatment of mental defects down through the ages beginning with the writing of a famous Egyptian physician in 2900 B.C.

Beall and Stanton<sup>16</sup> believe that since mongolism appears to a far more marked degree in children born to older mothers, the modern tendency for women to have fewer children must result in a diminution of the proportion of mongolian defectives.

Hooton (1943) states, "The air resounds with plans for a world of peace and economic security from the womb to the tomb, the several freedoms, and lives enriched by more and better gadgetry." He goes on to say: "The postwar planners will accomplish little unless they attack the evil that is rotting human fiber." He recommends medical and genetic supervision of marriages to prevent inferior offspring through heredity and environment; sterilization of the insane, feeble-minded, and habitually antisocial; subsidization of parents proved capable of breeding superior children, and intensive and extensive studies on human heredity.

Cantor<sup>17</sup> raises the question of "What is a normal mind?" We are often deceived by outward appearances, economic status, and emotional conflicts. Social maladjustments are vital factors and may become either assets or liabilities. He concludes that no one is "normal" and modern civilization is "neurotic." He emphasizes the tragic inadequacy of our present institutions to meet the needs of the people.

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## ELECTROENCEPHALOGRAPHY

JOSEPH HUGHES, COMDR., M.C., U.S.N.R.

EDITOR'S NOTE—*The use of the electroencephalogram has become one of the standard procedures in the investigation of certain neuropsychiatric conditions. Dr. Hughes has presented a brief review of the technic, findings and uses of the electroencephalogram.*

Since Berger's initial report in 1929 on the recording of the brain potentials by means of leads placed on the scalp, there has been collected a vast fund of information in regards to the clinical significance of these electrical changes.

For the development of clinical electroencephalography, reference may be made to the work of Gibbs and Gibbs (1941), and of Jasper (1941).

An electroencephalogram (EEG) records cortical electrical activity and is a useful diagnostic procedure whenever impaired cortical function is suspected. It is indicated clinically in the study of the following conditions: syncope, convulsive seizures, head trauma, cerebral vascular disease, brain tumor, infectious and degenerative diseases involving the cerebral cortex, such as meningitis, paresis, and Alzheimer's disease, etc. The psychoses and mentally deficient do not show abnormalities in the electro-

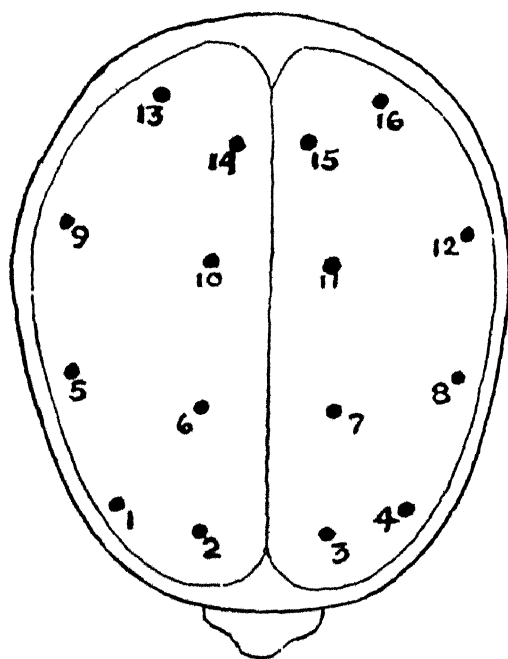


Fig. 1—Leads for complete exploration.

encephalogram unless these conditions are due to organic brain disease.

There is no preparation necessary for an electroencephalogram except that the patient should be free of sedation for forty-eight hours prior to the test if possible clinically. The technic for such an examination is as follows:

The patient sits quietly in a chair or lies down in a comfortable position; then lead electrodes are arranged on the

scalp over the frontal, rolandic, parietal, and occipital areas. The electrodes usually consist of flat metal disks, 5 mm. in diameter, held in place by collodion or by some other suitable means. These electrodes feed into recording amplifiers

complete exploration, sixteen leads will be required (Fig. 1).

At the conclusion of the test, the patient is asked to hyperventilate by breathing deeply through his mouth for a period of two minutes. As a result of this hy-

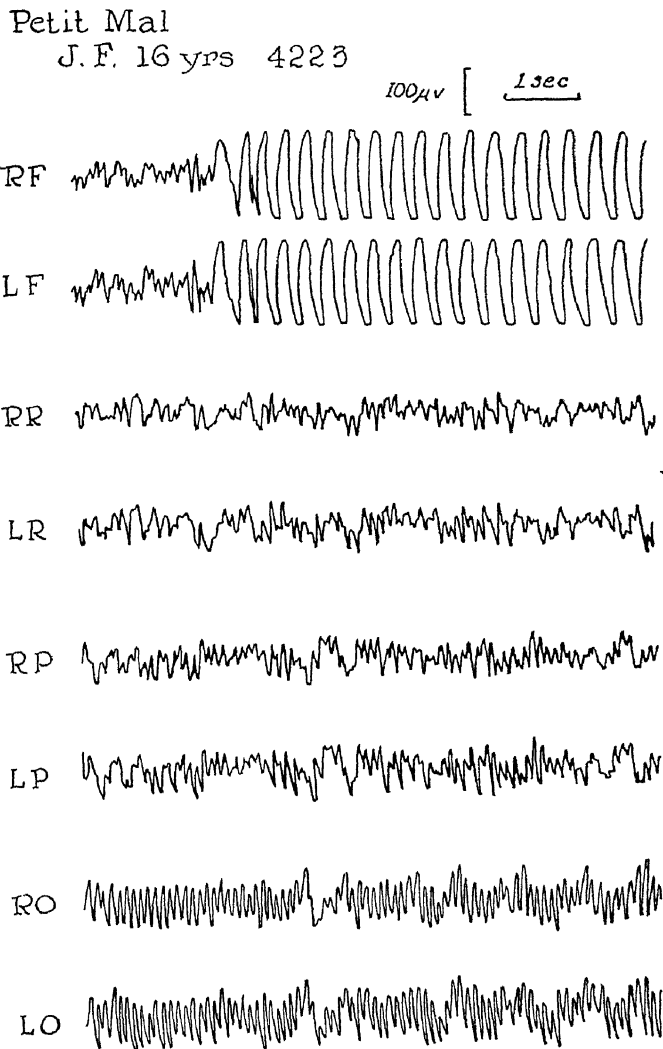


Fig. 2.

which in turn drive ink-writing electromagnetic pens, which record the cortical potentials. Homologous areas are recorded simultaneously from both hemispheres. For survey purposes, at least eight leads should be employed. For

perpnea and the blowing off of carbon dioxide, nervous system irritability is increased and latent EEG abnormalities may be disclosed. When there are gross abnormalities in the EEG tracing hyperventilation may be eliminated. The time

required to complete an EEG tracing varies from twenty to thirty minutes.

Two types of leads may be used in the recording, the monopolar or bipolar. In the monopolar technic, one electrode is placed on the scalp and the other on the

With the bipolar recording, the difference in the potentials between both leads is recorded.

It follows from this that since the monopolar technic reflects the total electrical activity it gives the greatest de-

Petit Mal associated with Hypoglycemia

J. McC. 23 yrs. 12793

100  $\mu$ V [ 1 sec ]

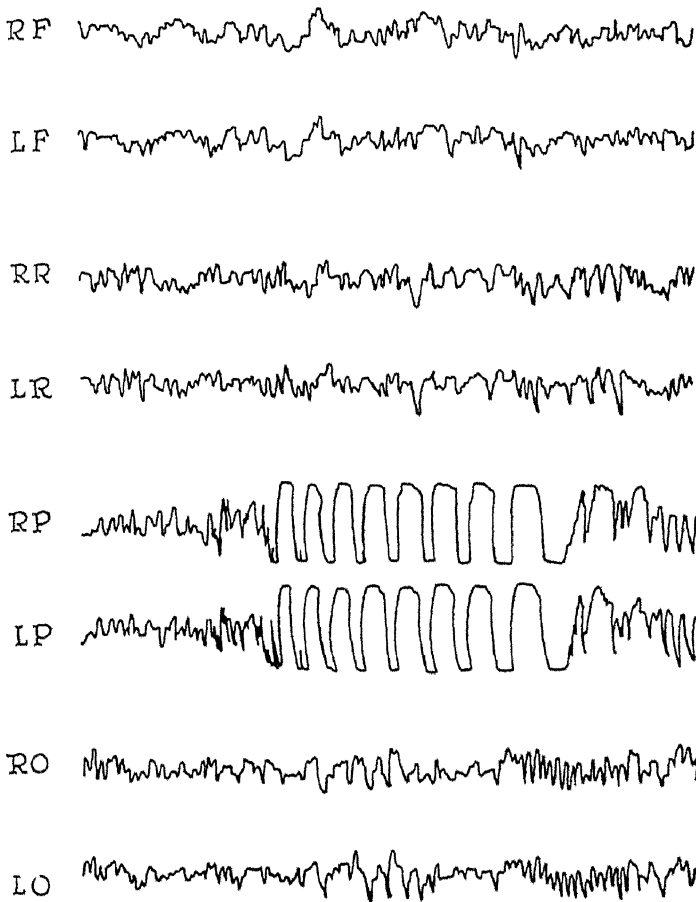


Fig. 3.

ear. The electrode on the scalp is referred to as the active lead, the one on the ear as the indifferent lead. In the bipolar technic, both electrodes are placed on the scalp. With the monopolar recording the total electrical activity occurring under the active lead is recorded.

tailed information, whereas the bipolar technic lends itself particularly to the localization of focal lesions.

A separate channel of amplification is required for each area recorded. An instrument with two channels of amplification will permit simultaneous record-

ings from the right and left hemisphere. This is the minimum required for clinical testing. For successful tumor localization, a three-channel instrument is required. A four-channel instrument is more than twice as efficient as two, a

Of these, a four-channel EEG is recommended as ideal for clinical use.

### Artefacts in the EEG

Artefacts to be watched for in an electroencephalogram are those occurring

Grand Mal

J.P. 33 yrs. 9573

100 $\mu$ V [ 1 sec.

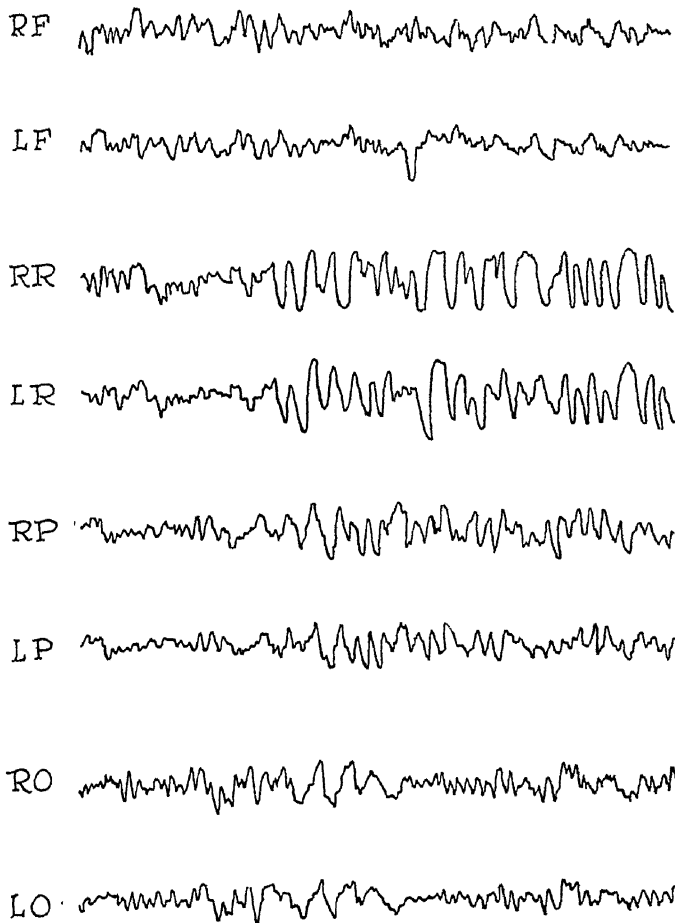


Fig. 4.

six-channel instrument permits the simultaneous recording of the frontal, parietal and occipital areas of both hemispheres at the same time and shortens the time needed for recording. For simplicity and efficiency an ink recording instrument is preferable to other models.

from faulty application of electrodes; from extraneous electrical activity; from movements of the patient including movements of eyes, clenching his jaws, swallowing, etc.; occasionally the QRS complex of the electrocardiogram may be picked up. Sweating results in a slow

rise and fall in the base line. This latter artefact is most troublesome in the frontal leads. All artefacts should be recognized at the time of the recording and so indicated on the tracing. If artefacts arise from extraneous electrical

sembled and tested before the question of special screening is decided.

### Interpretation of the EEG

**Normal EEGs**—A normal EEG may be defined as one in which the fre-

Astrocytoma. Right temporal-parietal lobes.

P.H. 57 yrs. 9574

100  $\mu$ v [ 1 sec.

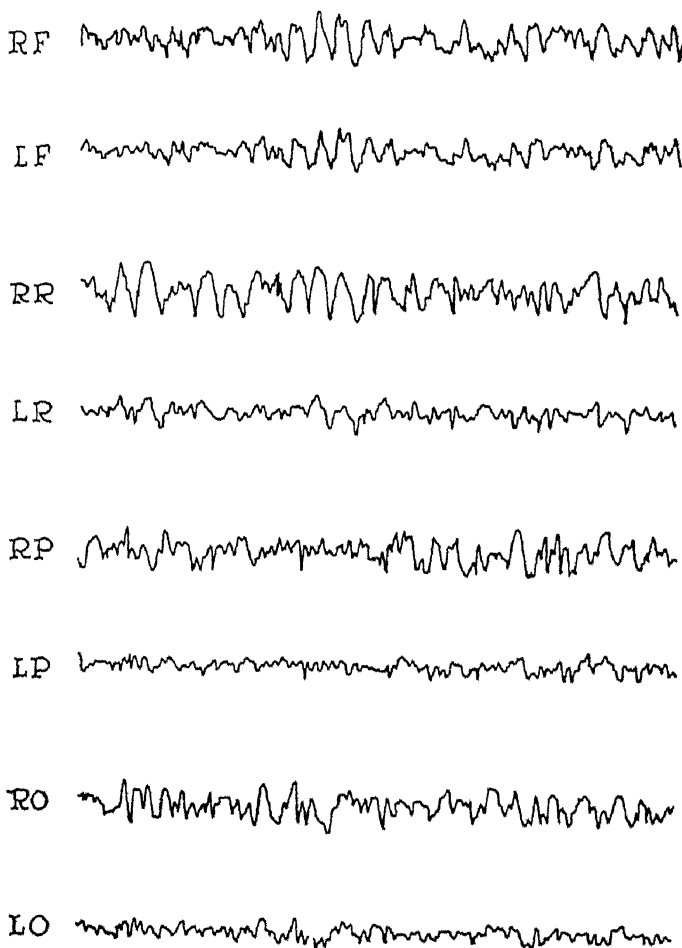


Fig. 5.

activity resulting from proximity to electrical equipment (diathermy, elevator motors, x-ray apparatus, etc.), it will be necessary to install the electroencephalograph in a shielded room. It is recommended, however, that the electroencephalographic equipment be as-

sembled and tested before the question of special screening is decided.

With children the following standard prevails: From birth to four years, there are frequencies varying from 1 to 4 per second; 4- to 6-per-second waves begin



appearing in the third year; from four to seven years, there may be random slow waves, 4- to 6-per-second waves, and the beginning appearance of 8- to 10-per-second waves; from eight to twelve years, the predominant frequen-

slow or too fast waves for the given age group or by the presence of focal abnormalities.

**Abnormal EEGs**—Abnormalities in the EEG are reflected primarily by a slowing in the cortical frequency.

### Melanosarcoma

O. J. 35 yrs. 13098

$\cdot 100 \mu v$  [  $\frac{1 sec.}{\text{---}}$  ]

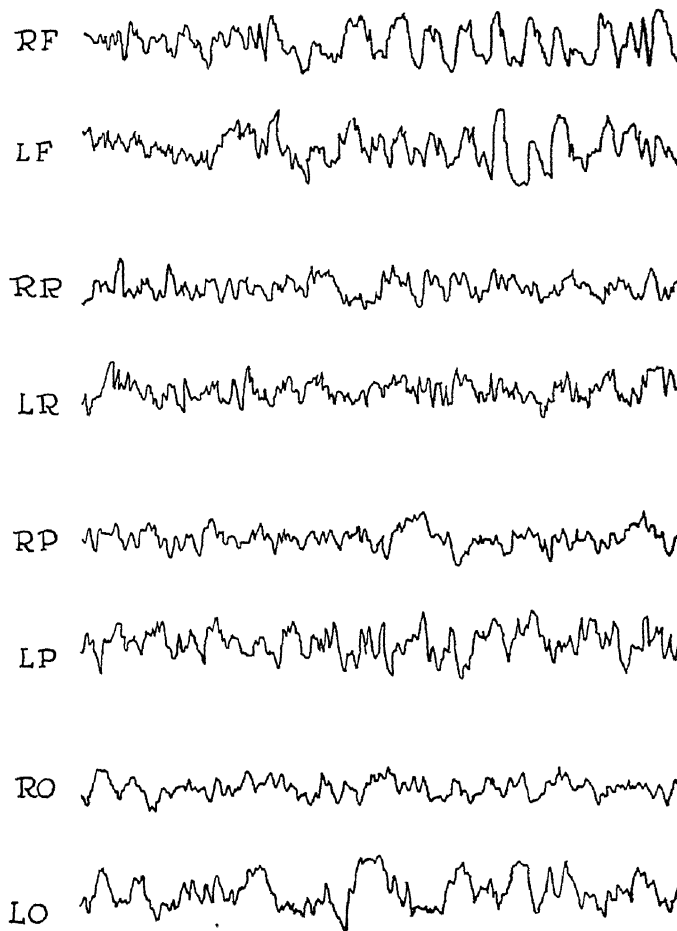


Fig. 6.

cies are of the adult type, but 4- to 5- and 6- to 7-per-second waves may continue to appear. The interpretation of EEGs in children is complicated by the normal appearance of the above mentioned slow waves. Abnormality is indicated by a predominance either of too

Changes of amplitude are of less importance. The abnormalities noted in epilepsy are as follows:

**Petit Mal**—The electrical abnormalities associated with this condition vary from spike wave formations to random slow activity. Whenever the spike wave

formation is seen, petit mal may be diagnosed. This type of activity may exist latently and only be evidenced after hyperpnea. (Figs. 2 and 3.)

**Grand Mal**—This condition may be reflected in the EEG by the presence

frequently seen around the periphery of cortical tumors. Focal brain damage, however, may be revealed by the appearance of diphasic spikes. The appearance of any of these above waves in one specific lead may be construed

Craniopharyngioma

C.C. 14 yrs. 12962

100 $\mu$ v [ 1 sec.

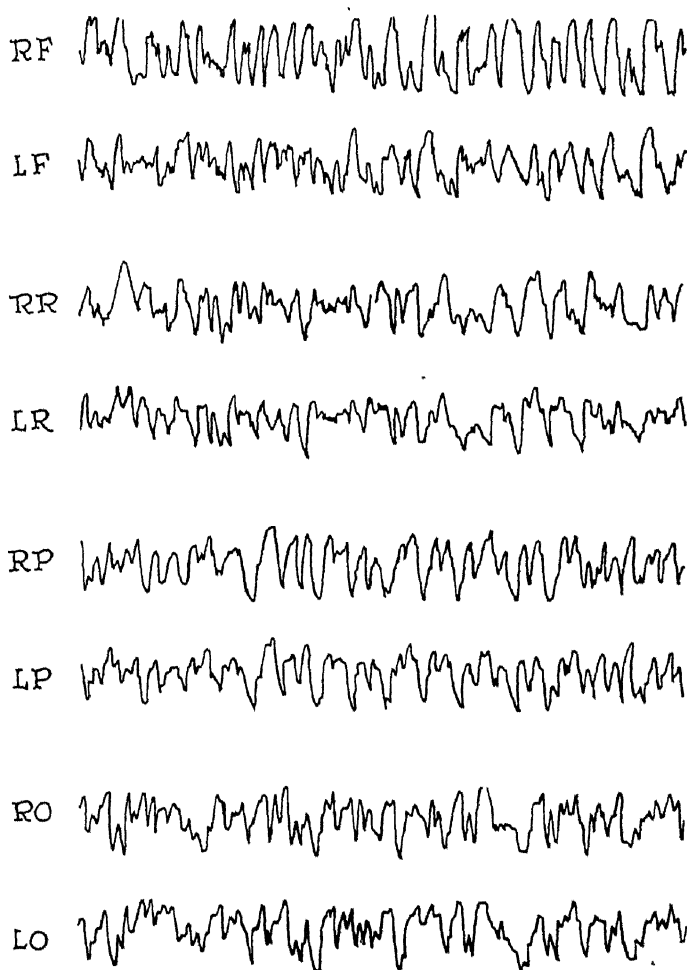


Fig. 7.

of very slow 3- and 4-per-second waves, or by random sharp waves, or very fast activity, or by random slow waves. (Fig. 4.)

**Focal Brain Changes**—Irregular slow waves, 1 and 2 per second, are

as evidence of focal changes. The EEG in cases of brain tumor is shown in Figs. 5, 6, and 7. Postencephalitic changes are illustrated in Figs. 8 and 9.

The EEG should be looked upon as an aid in neurological diagnosis. Nega-

tive findings can be expected in manic depressive psychosis, schizophrenia, involutional melancholia. Normal tracings are also obtained in the mentally deficient and in patients suffering from migraine and psychoneurosis.

of an inconstant variety. There is no pattern in the EEG that indicates the nature of the disease process except the spike wave formation seen in petit mal epilepsy. In all other instances, the electrical activity has to be interpreted in

Behavior Disorder, Postencephalitic

M.C. 15yrs. 13176

100 $\mu$ v [ 1 sec.

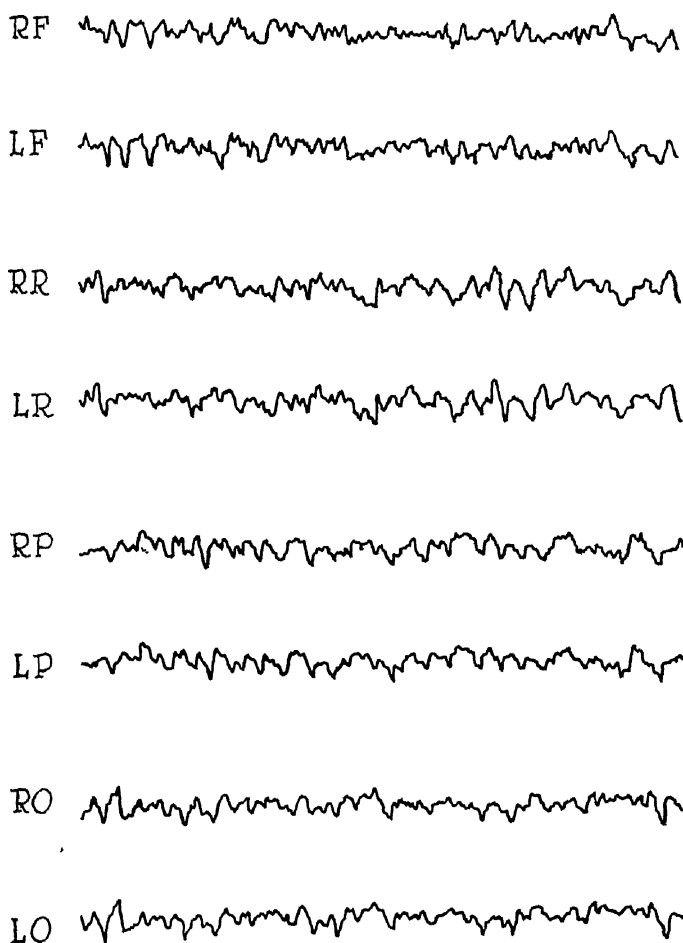


Fig. 8.

Positive tracings are seen in epilepsy, craniocerebral injuries, space-taking lesions, and in infectious and degenerative processes. About 20 per cent of children or young adults suffering from behavior disorders will also show abnormalities

the light of the history and clinical findings. In every instance, however, in which abnormalities are detected, the EEG will reveal whether this cortical abnormality is focal or whether it is generalized.

Obesity. Postencephalitic.

N.B. 31 yrs. 12632

100 $\mu$ v [ 1 sec.

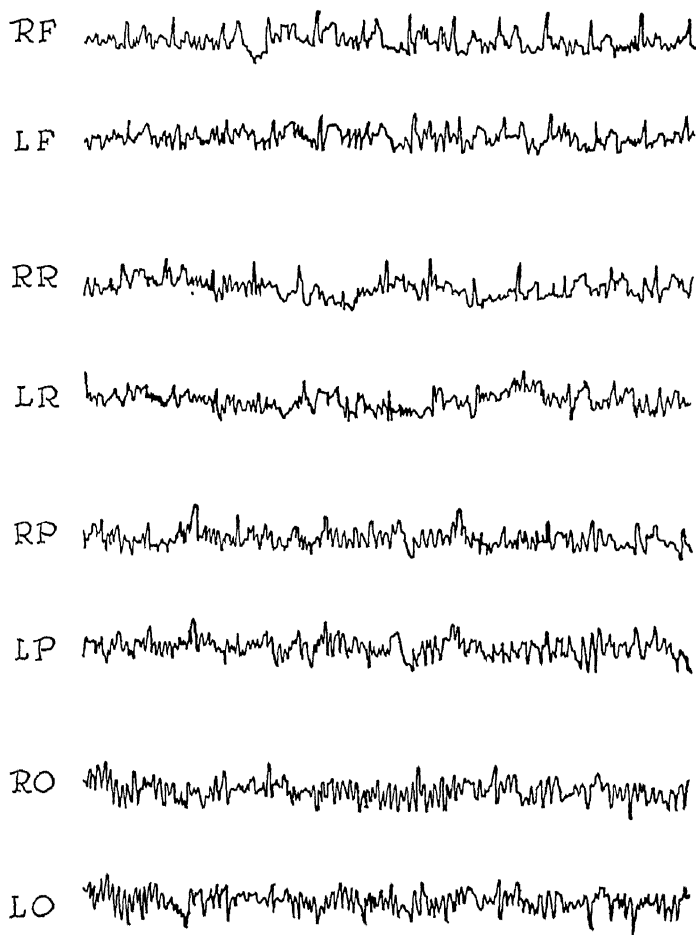


Fig. 9.

## NARCOANALYSIS

HERBERT FREED, M.D.

EDITOR'S NOTE — *Treatment in Psychiatry leaves much to be desired. Dr. Freed has presented a review of some of the most important new approaches to the therapy of these baffling conditions.*

The term narcoanalysis was first devised by Horsley in 1936 for the technic which utilizes a narcosis artificially induced by a barbiturate for the express

purpose of facilitating the analysis of a patient's mental content. More recently, Grinker and Spiegel,<sup>1</sup> of the Army Air Forces, have applied the term narco-synthesis to this therapeutic process after modifying the procedure and investigating its psychodynamic aspects. They say that under a state of seminarco-sis induced by intravenous sodium pentothal, a barbiturate, the patient is able to

live through his traumatic battle experiences. Under this treatment, the patient seems to synthesize, to put together the fragmented emotions and impressions connected with his experience, thus constructing a memory which corresponds almost completely with the original experience. Freed from the impact of the immense forces of the repressed emotions, the patient restores contact between the powerful inner emotional drives and the world of reality.

Anesthetics have been used to aid psychotherapy for many years. The discovery of the barbiturates, however, introduced a particularly useful group for psychotherapeutic work. Horsley, Grinker and Spiegel and others feel that the site of action of sodium amytal and sodium pentothal is the midbrain, particularly the hypothalamus. For this reason it is concluded that narcoanalysis or narcosynthesis thus differs from hypnosis in its psychophysiology. Certainly there are side effects, such as disorientation and drowsiness with confusion, which are not seen in the routine use of hypnosis.

The drugs of choice are sodium amytal and sodium pentothal. Grinker and Spiegel prefer the latter because the induction period is shorter and the duration of the effect is less prolonged. The dosage required for a satisfactory narcosis for either drug is the same, 0.25 to 0.5 gm. Alcoholics and patients with marked anxiety may take up to 1.0 gm. With the understanding that the patient has been psychologically prepared for the treatment, the drug is injected into the antecubital vein usually at the rate of 0.06 gm. (1 grain) per minute, while the patient is asked to count backwards from the number 100. When the speech becomes changed, usually thickened, often slowed, and perhaps before the

counting becomes confused, the injection is discontinued.

With a satisfactory level of narcosis, the patient will usually begin to speak spontaneously and he is allowed to proceed without interruption. Sometimes, however, the therapist suggests a certain topic, or tries to take the patient back to a particular age period, etc., just as in hypnoanalysis. Statements made to the patient should be short and simple with clear diction. The usual duration of such a treatment is about an hour.

Brenman and Gill<sup>2</sup> have recently published a monograph on hypnotherapy which adequately summarizes the general opinion on the use of drugs to produce the hypnotic state. They say: "This is usually a variety of the 'sleeping method,' the only difference lying in the fact that chemical means are employed in order to induce hypnosis when verbal methods have failed, or simply to accelerate it."

It should be noted that Grinker and Spiegel include in their procedure of narcosynthesis the aim to aid the patient in reliving his traumatic battle experiences. This is the equivalent of abreaction, the dynamic process which can take place in any type of neurosis and at any time when there is a reliving of repressed effect. While this is the term Freud applied to a very vital aspect of psychotherapy, Aristotle was aware of its value and used the concept of catharsis in connection with the release of pent-up emotions in an anesthetic experience.

Brenman and Gill observe that this "abreactive method," which has been used extensively in World War II, has usually been brought about by drugs rather than by the verbal methods of hypnosis; this is what is ordinarily described as narcoanalysis. In narcosynthesis the therapist takes a very active

part in helping the patient relive the experience, occasionally giving the inciting stimuli and often giving reassurance and support to lessen the patient's anxiety while he experiences again a harrowing memory which he now acts out. The therapist also reviews with the patient this experience when the latter is no longer under the drug's influence.

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### Thematic Apperception Test

The thematic apperception test known as the TAT is a method of investigating personality by analyzing stories which the patient is asked to "make up." In order to limit the stories to certain fields, a series of pictures is used as stimuli. They are, for the most part, pictures of people: of different ages, of both sexes, in different situations. Every possible chance is allowed for the patient to identify with a hero in the stories. He is asked to tell about the picture, make up an antecedent to the situation and also an outcome; and to describe (unwittingly, to the trained interpreter) his own feelings, strivings, fears, conflicts, etc., while he is telling about the hero with whom he is unconsciously identifying.

These pictures are deliberately made equivocal and unclear to allow more leeway for fitting the particular problem of the patient.

This is a projective technic, "projective" being defined in accordance with Freud's formulation as the ascription of feelings and qualities of one's own to other people as a defensive process, and without being aware of these phenomena.

The basic technic of the test was first described in 1935 by Morgan and Murray in their paper on "A Method for Investigating Phantasies." In the past ten years, this test has steadily gained in popularity. The brief manual which accompanies the test\* gives a satisfactory description of the purpose, administration and analyses of the stories.

At the present time it ranks with the Rorschach technic as the best of the projective methods. Indeed, in many ways the two are complementary. If one can say that the Rorschach test enables the examiner to determine the form of the psychological disturbance, it is safe to add that the TAT provides the content of the illness. Essentially, then, the former gives diagnosis while the latter supplies the psychodynamics. Murray states that "the subject leaves the test happily unaware that he has presented the psychologist with what amounts to an x-ray picture of his inner self."

The stories have been analyzed by different interpreters in varied manners. If one follows the system of "themas" described by Murray *et al.* in their significant and provocative book, "Explorations in Personality," one comes closest to what seems to be the most exact description of the personality to date. It is described in terms of forces, and delights the heart of one who feels that the goal of personology is to picture the personality in terms as precise as those formulated by the physicist.

However, it must be appreciated that every projective technic is a subjective technic. That is, it is a method that requires "rigorously trained critical intuition." Murray very sagaciously says: "The future of the TAT hangs on the possibility of perfecting the interpreter (psy-

\* Cards with Manual available through Harvard Univ. Press, Cambridge, Mass.

chology's forgotten instrument) more than it does perfecting the material." If the interpreter should project his own unconscious trends into his analysis of the stories, the conclusions could only be fallacious. On the other hand, if the subject becomes aware that he is identifying with a character in the picture, the responses usually have little value. Again, the subject may relate material that is obviously recalled from current moving pictures or books. This is not as revealing as the unconventionalized response which makes it apparent that one is touching the vital dynamisms in one's life. It can be deduced from this that the Rorschach technic has a vital place in dealing with subjects who present the last two complications.

Harrison, who is enthusiastic about the complementary aspects of the Rorschach test and the TAT, reports on a study of forty patients in the Worcester State Hospital. He did a "blind analysis" of these patients with a resultant validity of 75 per cent when the case history was compared with that formulated from the TAT responses.

Jacques reported a very recent study on 100 soldiers in the Canadian Army. He makes the significant statement: "The material obtained from the TAT was validated clinically in the sense that it was checked against material obtained on interview, free association, hypnosis, narcoanalysis, and observation of behavior in the rehabilitation program, and, most important, it was validated pragmatically from the point of view of usefulness in psychotherapy."

One of his conclusions was: "The use of the TAT is suggested . . . as a psychotherapeutic agent, both in the uncovering of dynamics and in the direct use of the stories in helping the development of the patient's insight into his problems."

These observations point up certain important aspects of this method. A valid report of the psychodynamics can be made without any additional history being made available to the examiner. Secondly, the stories can be used as starting points for free association so that when the test is given by the psychiatrist (who already is cognizant of the pertinent data in the anamnesis), the means for accelerating therapy often becomes apparent.

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### Hypnoanalysis

Hypnoanalysis was probably born in the first World War when Hadfield used a combination of hypnosis and re-education to treat neuropsychiatric patients. The aim in using hypnosis was to produce catharsis. He called the procedure "hypnoanalysis" and his results were satisfactory. Subsequently, he began to utilize the same technic with neurotic civilians. His orientation was psychoanalytic as an attempt was made to trace the symptom back to early traumatic experience.

The pioneer who laid the groundwork for hypnoanalysis as it is practiced today was another psychoanalyst, Simmel, who combined the technics of psychoanalysis with those of hypnosis. He stated: "A combination of analytic cathartic hypnosis with analytical conversations during the waking state, and dream interpretation carried out both in the waking state and in deep hypnosis, has given a method which on an average of two or three sittings brought about relief of the symptoms." His description of the battle casualty who relived the

psychic trauma is very instructive, since Simmel recognized the importance of the adequate release of aggression and provided dummies dressed in soldiers' uniforms on which the patient could vent his wrath. Not only was Simmel a pioneer; he was also a prophet, for he said of the civilian neurosis: "An analytic cure of the entire personality by a shortened and combined method will have to be reserved for the psychological clinic of the future."

One of the leading exponents of hypnoanalysis is Lindner,<sup>1</sup> who in his book defines it as "a technic compounded of psychoanalysis and hypnosis." As might be concluded, this could describe many variations of a combined procedure. Both Lindner and Wolberg, who have written the most recent book, "Hypnoanalysis," emphasize the period of training the patient in hypnosis which initiates the treatment. The first week of five to six sessions should find the patient receptive to the suggestion that he go immediately into a sleeping state. The attainment to the depth of somnambulism is desirable. (This training is similar to that described in many books on psychiatry.)

Lindner states: "Toward the close of the second week a patient or subject should possess a number of accomplishments which are prerequisites for successful therapy or research. He should be able to enter a deep trance almost as soon as he is instructed to do so; he should be able to revert memorially to earlier periods of his life; he should be able to verbalize while in the trance state; he should be able to carry out suggestions for posthypnotic behavior, especially as these apply to recall or amnesia. By this time, moreover, he will have entered into a reciprocal rapport with the hypnoanalyst that will bear

fruit in the work in which they will presently become engaged."

Much stress is laid on the avoidance of investigating the patient's emotional conflict prior to this training period. The fear is that this may stir up increased resistance on the part of the patient to becoming readily hypnotizable. Indeed, the actual hypnoanalytic procedure follows the next step which is the instruction of the patient in the technic of free association. With the beginning of this treatment the patient is seen daily. He initiates the treatment session by free association. Lindner induces hypnosis "immediately upon striking the variety of resistance which does not originate from the transference." Wolberg, on the other hand, always follows a brief period of free association with longer periods under hypnosis. In this latter period, he may make various hypnotic suggestions so that such technics as regression, dramatization, and dream induction may be utilized.

The induction of experimental conflict, automatic writing, hypnotic drawing, crystal gazing—these, too, are listed as hypnoanalytic procedures. For the therapist, they constitute a formidable array of methods of circumvention in resistance. It is not difficult to induce the patient to dream, utilizing posthypnotic suggestion. However, it should be noted that the analysis of the dream should be made during the trance state and not afterward. In the same way it seems that automatic writing, hypnotic writing, and crystal gazing are understood best when the unconscious mentation of the patient is closest to the perception of the doctor and the subject—during the hypnotic state. The induction of deep trance states, so that regression to an early age period occurs with the acting out of fantasies of actual psychic traumata, is not easy to attain except in certain subjects.



The induction of experimental conflict is an aid in promoting insight that seems to offer great promise. All of us are familiar with the production of experimental neuroses in animals. In 1935, Erickson produced an experimental neurosis under hypnosis in a patient which enabled him to recognize how the induced conflict applied to his chief complaint. The result was dramatically successful. Undoubtedly more use will be made of this technic in the future.

It can be seen even from such a sketchy description of the treatment that the therapist uses a psychoanalytic orientation with hypnosis as an aid in overcoming resistance. Lindner feels with Stekel that analytic therapy should be short and intensive rather than long and drawn out as it often is with the usual psychoanalysis. He therefore states: "Hypnoanalysis should last no more than three or four months, the final month being devoted to reorientation, exposition, and reeducation."

Wolberg<sup>2</sup> lists psychotic and prepsychotic individuals as subjects usually not suitable for treatment, although he gives a detailed account of the successful treatment of Johann R., who was confined to the chronic ward of a mental hospital with the diagnosis of hebephrenic schizophrenia. In addition, he feels that hypnoanalysis is not desirable in patients with character disorders of an extremely infantile dependent nature. Lindner is convinced that this therapy can be used in the psychopath and, if other workers should obtain equally satisfactory results, we have at last prepared the way for the solution of one of our most difficult psychiatric problems.

### Discussion

The dominant trend in psychiatry today is the drive to shorten psycho-

therapy. Hypnoanalysis, narcoanalysis, and the thematic apperception test have in common this aim—to shorten treatment with the aid of a dynamic form of psychiatry. Hypnoanalysis and narcoanalysis are technics of therapy. The TAT is the diagnostic technic that gives a rapid insight into the forces acting both within the personality and without, from the environment. Thus we may be enabled to perceive the conflict which has brought the patient into treatment. If one can avoid putting the patient through these special treatment procedures, thus not arousing his resistance or anxiety, the therapy has been accelerated markedly.

Sargent has made the following apt comparison of the projective methods which "might be regarded as the legitimate children of two parents: A brilliant and daring mother, psychiatry, and an equally intelligent but more conservative father, academic psychology. . . . They have a promising future but have not overcome insecurity engendered by the fact that each parent is inclined to berate them for faults presumably inherited from the other." This description readily applies to the utilization of hypnosis and drugs by the psychoanalyst. Freud states that "psychoanalysis . . . only began with my rejection of the hypnotic technic" and for a long time thereafter he and the psychoanalytic group avoided the therapeutic use of hypnosis. In the swing to a dynamic psychiatry, which depended upon free association by the patient with the therapist acting as a mirror and the patient gradually obtaining an undistorted view of himself, the use of drugs as adjuvants was also disavowed. This view is best verbalized by Hadfield: "The use of the drug is a crude though sometimes necessary assault on so sensitive an organism as the mind, and in spite of its abreactive

value, often leaves the more basic moral problems unsolved." Perhaps we are about to enter the era where we may successfully combine all of these methods. At least not only is the organicist but the psychoanalyst also experimenting with methods which indicate the acceptance of the unity of psyche and soma.

All psychiatrists have had the experience of observing therapeutic changes following a diagnostic procedure, which may be an interview or one of the "objective" tests like the Bernreuter personality inventory. This experience is even more frequent with the use of the TAT. Indeed, it has been our experience that it can be incorporated in the play technic with children. Adults, too, have been able to realize that their emotional difficulties and psychosomatic complaints can have underlying unconscious trends when these are objectified by recurrent themes in the stories they relate to the examiner.

The author feels that specialized technics can be practiced by one who has not had formal psychoanalytic training and that considerable benefit may be derived from their use. The book, "Men Under Stress," by Grinker and Spiegel should be read by everyone interested in narcoanalysis. It offers much more than a complete discussion of the use of barbiturates in the war neuroses, with an abundance of case material. The civilian application is kept in mind and outlined with lucidity. We, too, have been particularly eager to realize all of its potentialities for the neurotic civilian, and a preliminary report has been given on a selected group of cases. It was felt that the results were sufficiently promising to continue the work and make further reports.

We unthinkingly turn to the use of the intravenous administration of bar-

biturates because it is part of our routine medical training. With no more conscious thought do we shrink from a procedure such as crystal gazing to which clings that aura of charlatanism or from the routine use of hypnosis which has been relegated to the armamentarium of the vaudeville entertainer.

Wolberg's book makes us revise such attitudes and is a good text for the novice, while it sets a high standard for all who would widen the scope of dynamic psychiatry.

Lindner has restricted his discussion to the field of the psychopath, thus limiting its appeal for the general practitioner.

Jacque's report would seem to be the best of the latest papers on the TAT. The confirmation of the findings by other clinical procedures is gratifying. Of course, the very thorough personality study of the group of volunteers at Harvard Medical School reported in Murray's "Exploration in Personality" should be read by anyone desiring to check on the validation of test material. The forthcoming second volume of Rapaport's "Diagnostic Psychological Testing," which promises to include a complete section on the TAT, should also be worth reviewing.

In conclusion, it must be emphasized that the orientation is psychoanalytic throughout—with the understanding of the "unconscious" being paramount—but with the realization that "ego" psychology, formerly the stamping ground of the clinical psychologist, is now the domain of clinical medicine.

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## PSYCHOSOMATIC MEDICINE

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**Diagnostic Methods and Treatment in Psychiatry**

In evaluating the incidence of "psychosomatic affections" over the past forty years, Halliday<sup>1</sup> emphasizes that they comprise many of the chronic recurring forms of sickness, and that they "incapacitate rather than kill." He brings attention to two little known "key" phenomena: Sex shift and age shift. Exophthalmic goiter, which normally preponderates in females, has fallen from a ratio of 10:1 to one of 7:1. Diabetes, which during the late nineteenth century preponderated in males, in a ratio of 2:1, has become about twice as frequent in females. An opposite sex reversal has taken place in peptic ulcer, which prior to 1900 preponderated in females, whereas in 1940 it was nearly three times as frequent in males.

In a careful analysis of morbidity statistics, Halliday infers that in all the diseases showing an upward trend, "upsetting events" have been shown to be statistically significant as precipitating factors. These psychosomatic affections are distinguished by being causally associated with environment in its psychological aspects. On the other hand, it has been observed that war, in that it provides a common objective and diminishes social disintegration, might be expected to modify the incidence of some of these illnesses. This expectation is borne out by the definite decline in Britain, during both World Wars of exophthalmic goiter, suicide, and diabetes. Certain of the diseases which have increased in incidence show interesting interrelationships. "There is, for example, some kind of connection between psychoneurotic anxiety state, hyperthy-

roidism, and exophthalmic goiter; and the trio of peptic ulcer, 'fibrositis,' and hypertension is commonly found as associated, alternating, or sequent affections in the same individual, and the personality types of these disorders show certain corresponding characteristics."

On the other hand, the diseases showing a downward trend are distinguished by being etiologically associated with environment in its *physical* aspects — such as chlorosis and chorea.

Halliday's findings with regards to changes of sex incidence lead him to conclude that diseases which preponderated in females during the late nineteenth century (*viz.*, peptic ulcer, exophthalmic goiter, and essential hypertension) became increasingly manifest in males during the twentieth century, whereas the illnesses which preponderated in males (*viz.*, diabetes, suicide) became increasingly manifest in females. "This finding suggests, among other things, that the 'personality type' of males was becoming more feminine and that of females more masculine."

There is also evidence that a rising trend in the incidence rate (but not necessarily the mortality rate) of psychosomatic affections is accompanied by a retrogression of the age peak, *i. e.*, of the age of maximum frequency towards the younger age groups, and, conversely, a falling trend is accompanied by the age peak receding towards the older age groups. Such correlations would tend to suggest that certain illnesses "represent a function of the historical era and of the social setup in which persons happen to live and physicians to practice."

**Narcolepsy** — Although true narcolepsy has in the past been usually viewed

as due to organic causes, discoverable or latent, there have appeared within the past few years several articles by different investigators supporting the thesis of a psychogenic motivation for many of these attacks. Langworthy and Betz<sup>2</sup> present six carefully studied cases, and advance the hypothesis that narcolepsy represents "a personality reaction to an emotional issue," and view the etiology as entirely psychogenic.

Spiegel and Oberndorf<sup>3</sup> report one case studied intensively over a period of two years, which presented many of the mechanisms which relate this manifestation to a true neurotic genesis. This woman, aged forty-nine, evidenced brief periods of compulsive sleep as well as longer periods lasting up to thirty-six hours. She also gave evidence of hypnagogic hallucinations, cataplexy, polydypsia, as well as right-sided motor and sensory hysterical symptoms. No psychological conflicts were discoverable during the first year of hospital observation, even when hypnosis was resorted to. The first clues to her intense underlying emotional conflicts were indicated through terror dreams and no improvement was observed until confessional catharsis occurred. When eventually the nature of some of her conflicts became evident, transient attacks of sleep would be precipitated by having her consider some of the known distressing conflicts. Eventually, under tremendous emotional tension, she revealed an extremely traumatizing psychosexual situation to which she has been exposed for over thirty years centering around incestual relations. Following this final revelation, all her hysterical symptoms immediately became less severe and her attacks of narcolepsy cleared completely.

These authors emphasize the fact that the mechanism of falling asleep to evade difficult situations is a well-known re-

action. During catharsis, the patient's tendency towards drowsiness served as a valuable inverse indicator of the extent to which she was unburdening herself. Only as the somnolent tendencies as well as the conversion symptoms began to disappear did this woman display any strong conscious feeling of guilt about her past life situation. "The awareness of guilt and the attacks of narcolepsy seem to have been reciprocally antagonistic to each other." These authors compare psychogenic narcolepsy as a symptom with the well-known dynamic purposefulness of other true conversion hysteria symptoms, that of unconsciously satisfying forbidden wishes without the individual experiencing conscious guilt, and simultaneously acting as a punishment for these wishes.

**Sleep Paralysis**—Symptoms of hypersomnia, narcolepsy, cataplexy, hypnagogic hallucinations and sleep paralysis seem to be related phenomena. Sleep paralysis associated with combat fatigue has been reported in a series of twelve cases by Van der Heide and Weinberg.<sup>4</sup> Sleep paralysis is defined as a stage in which consciousness is awake while motor functions are asleep. It occurs when the patient is just about to fall asleep, or on waking up. The patient is unable to move any part of the body and tends to react to this with intense anxiety. This unpleasant condition may last from a few seconds to a few minutes. A touch may be enough to dissipate the reaction, though usually it disappears spontaneously. Although the symptom was precipitated by factors directly related to combat, more extensive studies proved that the symptom was more specifically related to the particular character and personality conflicts of the patient. Although all these patients were suffering from an emotional disorder precipitated by combat, nevertheless they

presented the common element of being intensely disturbed by confusion as to their emotional direction. "None of them felt free to let himself go in one direction or another, which would have caused him to be predominantly depressed, hostile, dependent or demanding. None of them was guided by one primary goal. These patients were outstanding for their indecisiveness and lack of goal-directed behavior. Part of their indecisiveness seemed related to a conflict about their passive submissive sexual needs." The authors postulate that the symptom occurs just prior to sleep, or on awakening, "in other words, at times when sexual urges are active, and controlled to a much lesser degree by the conscious restrictive or suppressive part of the personality."

Under psychotherapy, partial reintegration of the personality led to the disappearance of sleep paralysis in several of these patients.

**Syncope**—In discussing syncope as related to emotional stress, Romano and Engel<sup>5,6</sup> lay stress upon the existence of two quite different mechanisms involved in the loss of consciousness. The first type, vasodepressor syncope, is a vegetative neurotic symptom in which certain disturbances in the circulatory dynamics occur as the physiological accompaniment of the emotions of fear or anxiety. This type of reaction occurs most commonly in males and is often a "first time" phenomenon. The premonitory symptoms are weakness, sweating, nausea, sighing respiration, yawning, pallor, falling blood pressure, changes in the cardiac rate and rhythm, and finally loss of consciousness if the individual does not lie down. An EEG taken during the period of unconsciousness is invariably accompanied by high voltage slow waves. Consciousness is restored in the recumbent position. The second

type of reaction, hysterical fainting, appears to be the substitutive or symbolic expression of an emotion, "an attempt at a partial release of a chronic unrelieved emotional tension in which loss of consciousness is not related to any demonstrable disturbance of circulation or metabolism of the brain." It occurs most frequently in women. Loss of consciousness, which is usually abrupt, is not preceded by the premonitory symptoms of the first type of reaction. There are no changes in pulse, skin color, blood pressure, sweating, etc. The patient may remain unconscious for seconds or hours and there are no changes in the EEG during the period of unconsciousness. Furthermore, loss of consciousness is not related to position.

**Emotional Factors and Diabetes Mellitus**—Meyer, Bollmeier, and Alexander<sup>7</sup> have recently reported on two cases of diabetes mellitus treated by psychoanalysis while their diet and insulin requirements continued under very close clinical medical observation. Four to six quantitative estimations were carried out daily on sugar output in the urine. Both the patients developed their diabetes under the strain of an emotional conflict of striking similarity. Both subjects showed unusually strong tendencies to receive and to be taken care of. Both patients retained an infantile dependent and demanding attitude and felt intensely frustrated. Their demands for attention and love were out of proportion to the reality situation of an adult and consequently were never adequately satisfied. Their response to such frustration was intense hostility. The diabetes developed in both cases when these infantile wishes were frustrated by specific experiences, and the sugar output decreased when they temporarily denounced their demanding attitudes, or when the patients indulged in passivity

or self-pity. The hypothesis is advanced that "these food-demanding drives, under the condition when nobody is there to satisfy them externally, may turn to an autoplasmic type of satisfaction in a metabolic process which mobilizes glucose out of the glycogen stores of the body." An interesting correlation was the greatly increased sugar output during the night (independent of the carbohydrate intake) following vivid dreams characterized by high sexual tension and aggressiveness. The authors feel that their interpretation is in conformity with recent experimental findings that in certain cases of diabetes the rise of the sugar level is dependent not on failure of sugar utilization, but on excessive sugar mobilization. In both cases, the outbreak of diabetes occurred coincidentally with the tense emotional frustration which arose in relation to intense frustration on a psychosexual plane. In these two cases, *blood* sugar levels showed no clear correlation with emotional changes. On the other hand, the urinary output of sugar showed very definite correlation. A high sugar output in the urine appeared correlated with inhibited or repressed sexual tensions associated with increased repressed intense hostility, unexpressed either in word or deed. Low urine sugar levels coincided with predominant attitudes of self-pity and self-indulgence and when the intense desires to be fed or taken care of were being met by external circumstances. One case was able to complete analysis successfully, solved his major emotional problems, overcame his sexual immaturity, and married happily. Over a period of five years, his urine has remained sugar-free.

**Bronchial Asthma and Affective Psychoses**—Several authors have commented on the apparent antagonistic relationships between asthma and manic-

depressive attacks. Also it has been reported that patients suffering from bronchial asthma may present certain particular personality characteristics. Kerman<sup>8</sup> reports two patients who had suffered from asthmatic attacks for years and later developed manic-depressive illness characterized by acute depression. In both, the asthmatic symptoms disappeared during the course of the depression. Following electroshock, rapid remission was obtained but simultaneously, with recovery from the psychosis, the asthma returned in each case. No change in environment or alteration in exposure to allergens could be held accountable for the return of the asthmatic symptoms. The author reemphasized the conjecture which other experimenters have in the past advanced, namely, that both phenomena, manic-depressive attacks and asthma, may be manifestations—one more psychic, the other more somatic—of the same underlying psychic constellation, suggesting the apparent inability for asthma and manic-depressive attacks to coexist. Kerman's personality studies of his patients present the characteristics elsewhere described of the cyclothymic disposition, tending to mood swings and associated with paranoid features, much repressed hostility, and self-punishment drives. There is suggested an apparent antagonism between affective and allergic disorders.

**Cerebral Metabolism in Patients with Depression**—Himwich *et al.*<sup>9</sup> recently studied the cerebral metabolism in patients with depression by puncturing the internal jugular vein. Arterial blood was collected from the brachial artery. Blood samples were analyzed for oxygen and sugar. Thirty-three patients with depressive psychoses were studied. Examinations were made while patients were depressed as well as after recov-

ery as a result of electroshock therapy. The average value of the cerebroarterial venous oxygen difference was the same as for normal subjects. Cerebral blood flow showed apparently no change. The arterial venous glucose difference showed normal findings. Their conclusion is that the cerebral metabolic rate is normal in depression.

**Emotions and Blood Chemistry**—Diethelm, Doty, and Milhorat<sup>10</sup> have continued their investigations aimed at whether a relationship can be established between substances in the blood having adrenergic and cholinergic properties and specific emotional reactions. The findings demonstrate that during some specific emotions the blood contains factors that can affect the isolated duodenum of the rabbit in a similar way as does epinephrine or acetylcholine. Menstruation did not seem to affect the reaction. Anxiety, resentment, and anger are accompanied by definite adrenergic factors; tension and possibly fear with cholinergic factors. The authors emphasize that the results of such experiments are frequently difficult to analyze because often one is dealing with a combination of emotions which may each be of varying intensity and at other times subjected to intense repression. Distinct or pure emotions are infrequently encountered. When no disturbing emotions, such as anxiety or tension, were present, no changes occurred in the tracings.

**EEG and Psychoneuroses**—Although the electroencephalographic values for each patient with psychoneurosis are all within the normal range, yet the distribution of the particular data is not that of the normal population. Brazier, Finesinger, and Cobb<sup>11</sup> have reviewed the EEG's on 100 psychoneurotic patients, comparing them with those of 500 normal adults. The rhythms

are all within the normal range, and there is no abnormal wave formation or delta activity or wave and spike patterns. The most striking finding in the study is the bimodal distribution of dominant frequencies in the psychoneurotic group. The incidence of beta activity (18.0 cycles and over) was higher in the psychoneurotic group than in the normals. Anxiety neuroses had a normal distribution curve for dominant frequencies, but in a range faster than normal (11.2 as against 10.6 for normal).

**Glycine in the Treatment of Depression**—Good results are reported by Weinberg<sup>12</sup> in the treatment of mild depressions with *amino acetic acid* (glycine). Inasmuch as anorexia is a frequent early symptom, the lowering of serum protein may ensue. Restoration of the nitrogen balance also acts as a stimulant in increasing the patient's appetite. *Glycine* in the form of *elixir amino acetic acid* was used. The dosage was never higher than 6 gm. of glycine a day. Improvement, when it occurred, was noticed in a few days' time. Most of the nineteen cases treated recovered, some showed improvement. Two cases of involutional melancholia showed no benefit.

**Insulin Treatment of Schizophrenia**—The effectiveness of insulin shock therapy in the treatment of schizophrenia has had to be reevaluated through the ten-year interval since its introduction in this country by Sakel in 1936. Originally, Sakel reported a remission rate of 88 per cent in treated cases with a duration of illness of less than six months. Gralnick<sup>13</sup> recently published a seven-year survey of insulin treatment in schizophrenia. He referred to Bond and Rivers' (1942) five-year survey, which showed that although the immediate remission rate was 55 per cent, it

tended to level off to about 33 per cent in the second to fourth year after treatment. Gralnick's figures constitute the six-year follow-up of 554 treated cases. Of the 317 (60 per cent) patients paroled in 1937, 73 per cent were back in the hospital six years later. The success of the treatment, in terms of duration of parole, depended neither upon an increased number of treatments, nor on a greater number of comas. In the author's experience, although insulin has been of definite value in the treatment of schizophrenia, it has "by no means proved as effective as the early enthusiastic reports had led one to believe." Several findings stand out:

1. Worth-while results are obtained only in cases of a duration up to one or two years, and possibly three years.
2. Women respond better to the treatment than do men.
3. Treatment causes quicker remissions.
4. The age of the patient and the type of schizophrenia are not significant factors.
5. The number of treatments given and the comas produced bear no constant relation to the results obtained.

It is the author's impression that if a patient does not show definite improvement by the time he has had twenty-five to thirty treatments and half as many comas, that he will not become sufficiently well for discharge from the hospital no matter how many additional treatments and comas he receives. Furthermore, good remissions can be obtained with as few as sixteen to twenty treatments and relatively few if any comas. In spite of the extensive knowledge of the physiological effects of insulin, the author reemphasizes the fact that the exact manner in which it works as a therapeutic weapon in schizophrenia is still unclear. Gralnick emphasizes that

the psychological aspects of this drug type of therapy need much closer scrutiny. He expresses the conviction that "it is not merely insulin hypoglycemia that counts, but the specific insulin treatment situation. The fact that principally cases of short duration do so well is understandable only from this point of view. These patients are close enough to reality to respond to the treatment situation."

**Use of Sodium Amytal Narcosis as Prognostic Index of the Prospective Effectiveness of Convulsive Shock Treatment**—In a study of forty cases, Clark *et al.*<sup>14</sup> correlated the response of patients to intravenous *sodium amytal* with the eventual effectiveness of convulsive shock treatment (electroshock, or metrazol, or both). A 10 per cent solution of sodium amytal was injected slowly, the total dosage varying from 0.2 gm. (3¼ grains) to 0.6 gm. (9 grains). Of the fifteen cases which showed a good reaction to sodium amytal, thirteen recovered or improved greatly following convulsive shock treatment, whereas all five of those responding poorly did not recover. A good reaction to sodium amytal was constituted by the patient showing definite improvement in at least three of the four spheres of behavior, speech, mood, and insight. The authors point out that sodium amytal injections may act as a decisive factor in deciding whether shock therapy should be attempted in patients in whom the usual diagnostic criteria (prepsychotic personality, type of onset, duration of illness, nature of symptoms) are equivocal.

**Shock Therapy Modifications**—Although the proper use of *curare* has practically eliminated the danger of fractures occurring in electroshock therapy, nevertheless a sense of weakness following *curare* administration is alarming to



certain patients and at times results in their refusing to continue with therapy. In an effort to facilitate the handling of the resistive or apprehensive patient, Brody<sup>15</sup> has introduced the use of *sodium pentothal* in conjunction with curare. This combination of drugs makes for adequate narcosis and relaxation, reduces the risk of injury and obliterates postconvulsive excitement. Sodium pentothal acts more rapidly and for a briefer period than does *sodium amytal*. Whereas it produces excellent narcosis, nevertheless its relaxing effect is poor, and for this reason curare is used in conjunction with it. The recommended procedure is: 300 mg. of freshly prepared sodium pentothal in 2.5 per cent solution is injected intravenously in 30 seconds. Using the same needle, but another syringe, 0.45 mg. of curare per pound of body weight is injected slowly, taking a full minute. A few patients fall asleep, but most remain drowsy and cooperative. Four minutes after the injection has begun, the current is applied. Higher voltages or longer current time or both may be required. *Prostigmine* should be available as an antidote for excessive curare action. Subsequent doses of *pentothal* and *curare* may need modification, depending upon the depth of the narcosis and the strength of the convulsion at the time of the previous treatment.

**Electroshock Treatment of Acute Hysteria**—Although reports on the use of electroshock therapy of the neuroses are increasing, there is little mention of its use in major hysteria. Feldman *et al.*<sup>16</sup> report its successful use in two cases of acute hysteria. The first case, a woman of twenty-nine, presented an hysterical paralysis of both lower extremities, appearing as an aftermath to an automobile accident. Psychotherapy carried out in conjunction with *sodium am-*

*ytal narcosynthesis* had proven ineffective. She was given nine electroshock treatments and the paralysis cleared up gradually under this form of treatment. The other case was a clear-cut instance of sudden amnesia in a woman of thirty. *Sodium amytal narcoanalysis* was attempted several times without success, nor was any pertinent information elicited. *Sodium pentothal narcoanalysis* was likewise unavailing. During the five minutes immediately following the first electroshock treatment, the patient was able to recall her identity and other facts. The importance of psychotherapy in the complete treatment of these cases must nevertheless be strongly emphasized.

**Electronarcosis**—Although electro-narcosis has been studied experimentally in animals over the past forty years, it has only recently been introduced as a therapeutic measure in mental illness. Through the prolonged and continued application of an electric current to the brain, a controlled state of unconsciousness is achieved, preceded by a modified convulsion. Tietz *et al.*<sup>17,18</sup> report on its use in forty-seven cases of schizophrenia. Each case had been ill less than two years. Most of the patients selected had predominantly paranoid features, although some were of the mixed type. A 60-cycle alternating current of between 160 and 250 milliamperes was used. After thirty seconds, during which the patient has a tonic spasm, the current is dropped to 60 to 70 milliamperes, whereupon the patient usually shows clonic contractions. The return of respiration occurs at from 40 to 70 seconds, at which time an airway is inserted. At 60 to 75 seconds, when breathing is re-established, 5 per cent carbon dioxide in oxygen (carbogen) is administered by means of an anesthetic mask. The current is then raised gradually (5 milliam-

peres per 15 seconds) until inspiratory stridor develops. If stridor disappears, the current is then slowly raised again to a maximum of 125 milliamperes at the end of 5 minutes. In some patients the narcosis becomes more superficial towards the end of 7 minutes. In this series, the treatments were limited to 7 minutes. The patient is unconscious during the entire treatment, consciousness being regained within a few minutes after the current is cut.

As after other types of shock treatment, slow waves in the EEG pattern were observed, lasting often for about one hour after electronarcosis. With repetition of treatment these dysrhythmic patterns tend to persist, and in some individuals the dysrhythmia persists after recovery. These alterations are less marked in patients kept on 10 mg. of *thiamine chloride*, and 50 mg. of *niacin* throughout the period of treatment.

No frank fractures developed in this series. One case developed a mild compression of the anterior surfaces of two vertebrae without displacement. Cardiac arrest often of over 10 seconds' duration, due to vagus inhibition at the beginning of electronarcosis, may appear but is transient. Tachycardia may ensue as high as 160 per second, but appears to be without danger. Blood pressures reaching levels of between 190 and 260 have been observed but have not resulted in any demonstrable harm. Lowering of heart rate and of blood pressure has occurred promptly on discontinuing the current.

The majority of patients received between sixteen and twenty-five treatments. Treatment is given three times a week for at least four weeks until the patient's condition remains satisfactory for a week. Then two treatments are given the following week and a last treatment after one week's interval. If after

twenty treatments no improvement has been noticed, continuation appears to be without profit. The greatest number of treatments given to any one patient was thirty-nine.

Of the forty-seven patients, nineteen achieved complete remissions with insight; seventeen achieved a social adjustment with a retention of some personality defect; five showed only slight improvement, and six remained unimproved. Of the six failures, three were subsequently shown to have had previous attacks of schizophrenia and the other three showed marked hebephrenic features. A general improvement in the patients' physical condition coincided with the mental improvement.

In resistive patients, intravenous *sodium amytal* was resorted to without interference with the treatment.

The authors conclude that the results with electronarcosis in schizophrenia are definitely superior to those obtained with electroshock therapy and would view the therapeutic results with electronarcosis as approximating those of insulin shock therapy.

**Hypnosis and Suggestion**—The phenomena of hypnotic suggestion have been further studied by Spiegel *et al.*<sup>19</sup> because of the eventual value of hypnosis in the testing out of basic psychogenic hypotheses and for the excellent opportunity thus offered for the study of personality development. The subject is "placed at arbitrarily suggested periods of his life history (his birthdays) and tested in each of these regressed age levels by various standardized psychological procedures." In any earlier age level, the subject does not appear to have access to memory, experiences, and capacities which he had acquired in life later than the suggested age level. This "hypnotic ablation technic" is very similar to that of the experimental neurol-

ogist who ablates higher nerve centers, and thus releases the behavior qualities and activities of a lower neural level. The mental ages scored during the suggested regressed age level coincided very accurately with the so-called hypnotic age level. Using this technic, each age level was effectively studied for the quality and degree of integration of the individual's capacities for adaptation.

Lipkin *et al.*<sup>20</sup> have presented some interesting observations on the effects of suggestion in the treatment of vasospastic disorders of the extremities. Many physical methods of treatment have been suggested in the past (*e. g.*, intermittent venous occlusion, papaverine, mecholyl, histamine, sympathetic nerve block, vitamin B fractions, suction pressure, tissue extracts, estrogenic substances, etc.). Many of these have proven of definite value, but the variability of the results in different clinics suggested the desirability of evaluating the rôle of possible coexisting psychological factors associated with these physical therapeutic measures. This point is of particular importance in diseases of the small arteries since their response to vasomotor impulses is strongly influenced by emotions. Using the type of apparatus employed for iontophoresis and without recourse to verbal suggestion, the authors treated nine cases of vasospastic disorders with excellent subjective and some objective response in six of the cases. The patient was subjected to alternating "wet" and "dry" treatments, the apparatus being never turned on, or with a minimal current. On some occasions, *isotonic saline solution* muscular injections were also employed. Skin temperature readings, using a Leeds and Northrup thermocouple, were recorded. It was discovered that in several cases prolonged vasodilatation lasting many hours was achieved merely through the

suggestive effects of treatment, results equivalent to the effects of injected histamine, papaverine, or mecholyl. Objective changes, such as altered capillary blood flow, also followed the use of suggestion. Relief of vasospasm over a period of several years was achieved in several cases. In at least two cases subjective improvement was present after a year of no further treatment. Prolonged vasodilatation, with hands becoming pink and dripping with perspiration, was observed for hours after treatment. The observations confirmed the fact that skin temperature may change rapidly under emotionally charged stimuli, and cold seemed sometimes less important than psychic trauma in precipitating acute spasm. Altered capillary flow occurred after suggestion in several instances. The authors claim that the results obtained with suggestion are comparable with those obtained by any reported method of treatment, excepting perhaps surgery. Nevertheless, they specifically emphasize that they do not advocate the use of suggestion as a standard form of therapy in vasospastic disorders. Their findings emphasized the need for adequate controls in evaluating the therapeutic results in vascular disorders in which spasm plays a part.

**Prefrontal Lobotomy**—Commenting upon the fact that "anatomically, the normal brain in schizophrenia is one of the greatest mysteries of psychiatry," Freeman and Watts<sup>21</sup> report on fifty cases that have been subjected to prefrontal lobotomy from two to seven years previously. They mention that social adjustment is sometimes better at the end of five years than it is two or three years after operation. The word "recovery" is used with caution since "in undergoing prefrontal lobotomy the patient may exchange one psychological deviation for another." But the resulting

deviation frequently interferes much less with his social adjustment. On the other hand, a number of patients who have remained unimproved or who have relapsed following lobotomy have shown much better results following a second more extensive operation. In determining the likelihood of operative success, the emotional response of the patient is by far the most important criterion. Age, duration of disease, physical condition play only a negligible rôle. Emotional deterioration can best be judged by the facial expression and by the state of sympathetic tonus as manifested by pupils, pulse, and peripheral circulation. Favorable indications include excitement, resistiveness, stupor, destructiveness, whereas docility, weakness, and true apathy are definite contraindications. The authors remark: "While a patient is still fighting his disease, prefrontal lobotomy offers a chance for relief."

The results of prefrontal lobotomy are best in the severe anxiety states, in the involutional depressions, in the excessive tension states. Schizophrenias present a more difficult problem in terms of likelihood of success. The farther anterior the incisions are made, the less alteration there is in the behavior of the individual. Thus in schizophrenia, in order to successfully abolish the emotional charge attached to the abnormal ideas, incision has to be made somewhat farther posteriorly to the plane of the coronal suture, but there then occurs an increasing attendant risk of severe disability in the social adjustment of the patient. Accordingly in schizophrenia, a more extensive operation may be necessary if an incision in the plane of the coronal suture does not sufficiently improve the patient's condition. Surgical convalescence from an extensive operation is slow. The loss in initiative is

especially notable, and the patient may be unable to care for himself for a month or two.

Postoperatively, the persistence of hallucinations and delusions is of little importance in estimating the chances of recovery. If the patient no longer is preoccupied with them, this is a good sign. Although a certain number of patients do not achieve social recovery, they are often helped to much better adaptation to the hospital environment as a result of the surgical procedure. Of the fifty schizophrenics reported on, more than half are usefully occupied, and less than one in five remains institutionalized. Prefrontal lobotomy interferes relatively little with the individual's intellectual capacity as measured by standard tests. As the authors conclude: "Prefrontal lobotomy bleaches the affect attached to the ego and turns the patient's interest away from himself and towards the outside world." Although pathological ideational processes may continue, they lack their emotional charge and therefore cause little concern to the patient. Emphasis is placed on prefrontal lobotomy as a procedure of last resort, but this does not mean that it should be delayed until emotional deterioration has set in.

Kindwall and Cleveland,<sup>22</sup> in reporting on fifteen patients subjected to psychosurgery, make the observation that although the patient is not the same as before the mental illness, he is usually happier, more outgoing, and more at ease; often he is productive, and sometimes even more productive than before. In many cases, however, the illness can only be said to have been arrested, not eradicated. Though happier and easier to live with, the patient is not as able or complete a person as before his illness. The fifteen cases reported presented a wide variety of symptoms, from appar-

ent psychotic deterioration to chronic nonpsychotic tension states. In each case the prognosis had been viewed as hopeless, and most of them had been hospitalized for many years. All but four had received one or more forms of shock therapy. One patient is gainfully employed, five others are now living with their families, comfortable and socially acceptable. None of the fifteen was made worse and all showed some degree of improvement. The surgical dangers are: immediate or delayed hemorrhage, visceral and thermoregulatory disturbance, postoperative pneumonia, infection, and inhalation of unswallowed food. An occasionally observed complication consists of edema, blister formation, and sometimes tenderness and pain in one or both feet or legs, usually appearing during the month following lobotomy. The authors feel that the mental syndromes benefited by lobotomy are multiple and that the common factor effected by surgery is connected with the allaying of anxiety.

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## OCCUPATIONAL THERAPY

HELEN S. WILLARD, B.A., O.T.R.

OCCUPATIONAL THERAPY  
IN THE RECONDITIONING  
PROGRAM OF THE U. S. ARMY<sup>1</sup>

Occupational therapy has been recognized as one of the three sections, together with educational and physical reconditioning, of the total reconditioning program which has been developed in the hospitals of the U. S. Army.

The primary purpose of the reconditioning program was to accelerate the return to military duty of convalescent

patients in the best possible condition. Failing this, the aim was to prepare the patient for return to civilian life in such a way that his readjustment would be as effective and complete as possible.

Occupational therapy is defined as "that form of treatment characterized by assignment to purposeful physical tasks and prescribed by a medical officer." Its scope is fourfold: (a) Diversional therapy, which includes any avocational activities in which the patient

may indulge. These range from simple crafts and hobbies to music, photography, or motor mechanics. (b) Functional therapy, which is prescribed as directed exercise for the restoration of function of muscles and joints and toward the improvement of the general physical and mental condition. (c) Industrial therapy, which utilizes useful everyday work situations such as painting, sawing wood, or gardening. (d) Prevocational therapy, which includes prescribed exploratory shop processes planned to develop aptitudes and interests in a specific occupation and so to serve as a basis and guide for further vocational training.

Emphasis is placed upon the necessity for medical guidance and the employment of properly trained and qualified occupational therapy personnel.

### **Occupational Therapy for Physical Injuries**

In physical injuries there are three main disability groups: (a) Joint limitation; (b) muscle weakness; (c) incoordination. Treatment is based on the fundamental principles of physical treatment as applied in physical medicine: (a) Graded force for joint limitations; (b) graded resistance for muscle weakness; (c) muscle reeducation for incoordination.

All treatment should be coordinated with physical therapy, beginning the latter in as early a stage as possible, accompanied by occupational therapy when active motion is indicated and then discontinuing physical therapy and increasing the graded activity and resistive motion of occupational therapy. Fundamental posture principles are observed and it is the therapist's task so to adjust the work that compensation or substitution of uninvolved parts for the part being treated can be avoided save in cases of permanent disability, in which

substitution is indicated. Fatigue must also be carefully watched.

Accuracy of treatment in range and direction of motion, and the degree of physical exertion required, is achieved by adjustment of the position of the patient and the work and by special adaptations such as builtup tool handles, special pedal attachments for the bicycle saw, and spring resistance for looms, saws, or printing presses. Special equipment should, however, be considered merely a temporary expedient in grading activity toward normal use of standard equipment.

The basic principle of occupational therapy in cases with limitation of joint motion is graded stretching. Due attention must be paid to prolonged pain, increased or persistent swelling, loss of joint motion, and open lesions. Joint measurements should be made at regular intervals.

In muscle weakness with central, cerebral, or peripheral nerve involvement, graded resistance, with gravity eliminated by sling suspension of the injured part, motion against gravity, as in working with arms raised high, or with outside resistance, as in operating a press with spring attachments, is the basic principle of treatment. Muscle tests should be made at regular intervals and fatigue, overstretching and avoidance of injury to anesthetic areas should be carefully watched. Pollock<sup>2</sup> states that occupational therapy is particularly valuable in treatment of nerve injuries because of the long time required to effect recovery. Treatment should fulfil two requirements; first, that which hastens recovery; second, that which is of benefit to the patient in the use of a part in which complete recovery does not take place.

Incoordination should be treated by muscle reeducation, progressing from

motion of large muscle groups to training in accurate single joint and combined motions.<sup>1</sup>

**Thoracic Disorders**—In the treatment of thoracic disorders, which result in joint limitation, muscle weakness in thoracic and shoulder areas and general body weakness, occupational therapy should provide: (a) Activity without increase of respiration. *Example*, fly tying which requires no shoulder motion. (b) Activity with increase in respiration. *Example*, bicycle sawing. (c) Activity to increase muscle power and range of joint motion in secondarily involved areas. *Example*, gardening. Special attention must be paid to temperature, fatigue, drainage, and substances irritating to the respiratory tract.

**Cardiac Disorders**—Cardiac disorders require controlled activity to combat restlessness caused by anxiety and boredom. Activities should provide graded occupations ranging from bed work involving light finger motion only to ambulatory activity such as plant culture.

**Blindness**—Blinded persons need training to develop tactile and kinesthetic sense and space perception. Activities such as typing, cord knotting, and weaving may be used to create a high standard of precision in workmanship. Special precautions should be taken to familiarize the patient with his environment, to avoid excess of sympathy, and to emphasize independence.

**Treatment of Amputees**—The purpose of occupational therapy in the treatment of amputees is to promote mental health as well as physical restoration. The psychological shock of the injury may be lessened by early treatment which aims to maintain good social adjustment and to begin reeducation. Various crafts such as printing, carpentry, and model construction, and recreational

activities such as darts and ping pong develop skill and dexterity and reestablish confidence. After the prosthesis has been fitted, work should be planned so that the patient learns how to manipulate his appliance and is guided, through his own efforts, to make the greatest possible use of it. The occupational therapy department should be a proving ground where the prosthesis may be tried out, observed, and checked under actual working conditions.

In partial amputations of the fingers, the patient should work to increase mobility and power of the intrinsic muscles of the hand. Builtup tool handles may first be used and reduced in size as flexibility of the fingers improves. Clay modeling, leather tooling and lacing, typesetting, and fly tying promote coordination and skill.

Learning to write again is one of the most important things in the treatment of amputations of the dominant hand. If the patient is taught to write with the remaining hand, daily practice is essential. Large sweeping arm motions and easy rhythm should be emphasized with progression from blackboard to large sheets, ruled, then unruled, and so to ordinary paper. Practice should be interspersed with other more interesting activities. Letter writing should be encouraged. Proper writing position should be maintained at all times.

If the patient is to be taught to write again with the amputated arm, a cuff attachment holds the pencil in proper position. Writing is done by a rotary motion from the shoulder. The advantages of this cuff method are its naturalness, ease, and speed of learning, and the maintenance of the patient's thinking in terms of two-handed action. There may, however, be delay in starting reeducation because of sensitiveness or other injuries to the arm. For short

forearm and upper arm amputations, or for shoulder disarticulations, the use of the cuff may be difficult or impossible.

The use of bilateral crafts and activities promote coordination. There should be special practice in the use of all the appurtenances of daily living such as eating utensils, door knobs, shoe laces, telephones, razors, and the like.

Patients who have lost the secondary arm, that is, the alternate to that in which the handedness occurs, need particularly to be given bilateral activities lest they use the normal hand to the exclusion of the prosthesis. Typing, woodwork, billiard playing, eating, and personal care develop normal use.

Bilateral amputees need, primarily, treatment which will reestablish their independence. Adapted cuffs permit such patients in the preprosthetic stage to play ping pong, to turn pages of a book with a pencil held eraser end down, to hold eating utensils or tools. Skill in the use of prosthetic appliances will develop rapidly if the patient has had early experience which has encouraged him to practice and experiment. The main object is to foster morale and develop ease in everyday living but the patient must learn to do things in his own way and must master control of shoulder and back muscles, angle of hook and direction of approach. Special equipment and apparatus should be avoided if full independence is to be attained.

Additional handicap, such as partial or total loss of sight in the bilateral amputee, requires specialized training and individually designed apparatus. Raised margins on the paper serve as guides and facilitate writing. Development of coordination and skill must be emphasized and much depends upon the attitude and perseverance of the patient.

For lower extremity amputees, a planned program of diversion is needed

following surgery to promote the patient's mental wellbeing and adjustment to his handicap. The use of a floor loom, bicycle jig saw, or treadle printing press helps to strengthen muscles. Games such as shuffleboard, horseshoes, and bowling help to establish balance and gradually increase weight tolerance and proficiency. The teaching of correct use of the prosthesis is handled by the physical therapy department but occupational therapy activities should supplement such training.

An achievement chart provides objective measurement of the patient's ability to use the prosthesis, encourages wearing it at all times, and insures the satisfactory manipulation of it before the patient is discharged from the hospital.

### **Occupational Therapy in Neuropsychiatric Disorders**

Barton<sup>2</sup> states that occupational therapy should be used at all points of treatment in military service from the forward echelon aid station to the last point of evacuation in the psychiatric section of a general hospital. As soon as the acute mental upset is allayed, the soldier should be directed to useful work in the interest of his group. Idleness leads to slackening of morale and morbid introspection, whereas a concrete task to be performed releases tension and maintains morale.

Occupational therapy must fit in as a part of the whole reconditioning program and must be based upon the personality traits, cultural background, intelligence, aptitudes, and psychiatric clinical status of the individual. The goal must be concrete and clearly defined, the patient must have reasonably adequate means of achieving it, and must feel that he has a personal responsibility in so doing. Inconsequential activities should be avoided by work calling for initiative, imagination, and creative effort such as woodcarving, leather work, model boat and



plane building, fly tying, and block printing, which are recognized hobby outlets and offer effective means of arousing real interest. Painting, designing, newspaper editing and production, photography, and innumerable industrial activities may be graded in steps and may become acquired skills useful both in the Army and in civilian employment. It is advisable to provide different shops in which patients may be treated so that there may be segregation of cases needing a quiet, restful atmosphere from those who react better to active, robust projects such as carpentry, metal work, and printing.<sup>1</sup>

A well-lit room, approximately 30 x 40 feet in size, is adequate for the care of about twenty-five patients. One qualified occupational therapist is necessary but she can utilize trained corpsmen or Red Cross assistants and thus make adequate service available for larger numbers. One therapist and two assistants can supervise fifty patients daily in shifts of twenty-five each. Occupational therapy may be started anywhere and under all conditions with salvage material and a few tools, utilizing available assistants under supervision and guidance. A medical officer should organize, direct, and supervise the occupational therapy department. The trained therapist, provided by the doctor with a diagnosis and treatment of objectives, can translate the doctor's prescription into an activity which interests the patient, meets his needs, and brings about improvement.

Occupational therapy not only benefits the patient but promotes cooperation and a cheerful, friendly atmosphere which helps to maintain orderliness and discipline and to reduce destructiveness and the need of custodial supervision.

The vast majority of neuropsychiatric cases in military hospitals are psychoneuroses, especially the anxiety states

resulting from combat and being returned from overseas. Immediate treatment is of the utmost importance in order to prevent aggravation of the symptoms and prolongation of hospitalization. Patients are given an active program of physical and educational reconditioning and occupational therapy. The atmosphere must be permeated with expectancy of recovery and the patient must realize that the program is prescribed as treatment, that he has a share in the responsibility of getting well, and that he must also continue responsibility to the group.

All of the various types of occupational therapy activities apply in the treatment of the psychoneuroses. The choice of work projects for particular patients should be determined by an understanding of the dynamics of the illness which the doctor interprets to the therapist. The work selected should meet a specific psychological need. Projects such as radio work, wood and metal work, printing, motor repair, and business administration may promote correlation between occupational therapy and study interests. Purposeful activities encourage acquisition of new skills and develop group interaction.

Psychopathic personalities who adapt themselves poorly to the regimentation and team play required in the Army usually adjust readily in the occupational therapy shop. Carpentry, radio, electricity, automotive mechanics, printing, and graphic arts may uncover interests and aptitudes and develop a basis on which to build. Mental defectives stimulated by liberal praise and the effective accomplishment of short time projects, such as leather work, plastic crafts, metal work, weaving, or simple carpentry, may be restored to society as useful though limited members. Psychosomatic disorders may be benefited by both diversional and functional occupational

therapy and psychic barriers to recovery may thus be removed. Neurological problems such as posttraumatic conditions, complications of infections of the nervous system, and convulsive disorders require attention to both mental and physical factors. Graduated occupational therapy helps to improve function and to restore the patient's confidence in his ability to perform useful work.

In the treatment of the psychoses, occupational therapy serves to reestablish in the depressed patient feelings of personal value and achievement and stimulates outside interests. Arts and crafts are usually most acceptable and should consist at first of small units easily achieved so that there is little chance for bewilderment or lack of concentration and interest. Industrial work may be helpful and, at times, menial work may assist the individual who suffers from feelings of guilt and desires a means of expiation. There is need for constant guard against suicide.

Excited patients may be best treated by industrial work, gardening, salvage, or construction jobs which give opportunity for vigorous bodily exercise with sufficient space so as to avoid the friction and irritations of close contact with other patients.

Schizophrenic patients need stimulating group activities such as the publication of a news sheet, industrial work, or gardening, which may develop interest and initiative and serve to recall them from their dream world. Music and creative art may give some patients great satisfaction and benefit.

The paranoid individual works best alone; hence, individual work, especially with assignments of trust, such as work in the finance office, library, medical supply office, or as operator of the hospital public address system, may recreate a true sense of self importance. A

high standard of excellence should be encouraged in hobby interests, art projects, or job assignments.

**Diversional Handicraft Activities**<sup>1</sup>—Diversional activities comprise recreational interests such as arts and crafts, music, dramatics, and hobbies. They divert the mind from thoughts of illness, constructively utilize leisure time, stimulate interest, maintain morale and initiative, and conserve good work habits.

In the Army hospitals, the American Red Cross has provided for most of the diversional activities under the supervision of the Occupational Therapy Department. All arts and crafts and allied handicrafts or activities, painting, cartooning, clay modelling, wood carving, photography, music or dramatics, and many other projects have proven useful. Activities may be carried out in bed, ward, or shop with due regard to good posture, good lighting, avoidance of irritating materials or disturbance of casts or orthopedic apparatus and suitable selection of occupation for the individual patient.

**Industrial therapy**<sup>1</sup> is defined as the use of an industrial assignment or work project for its therapeutic effect. It may, therefore, be used for both mental and physical needs to stimulate alertness, reestablish work habits, increase work tolerance, combat effects of long hospitalization, and exercise specific parts or the whole body.

Employment under prescription in the utility shops, motor pool, laboratories, supply offices, or gardens gives the patient opportunity to contribute to the maintenance of his own community and so to take the first step toward resumption of normal life. Placement in job assignments must be made with a clearly defined purpose and the patient should understand the relationship between the work to be done and his recovery. Only

so long as the occupation benefits the patient does it continue to be of therapeutic value. Close supervision is necessary to insure that such treatment does not deteriorate into cheap labor. All jobs must be analyzed, work standards set up, and patients assigned in accordance with their needs and abilities. Industrial assignments may be connected with the educational program. There is opportunity to explore aptitudes and interests, to coordinate shop work and classroom instructions, and so to provide a basis for vocational training for those whose handicap makes retraining necessary.

In the military hospitals there has been great opportunity to develop a wide range of occupations as treatment methods. There is no question that occupational therapy should be practical and purposeful. Yost,<sup>8</sup> however, points out that curative value lies in anything in which one permits oneself to become truly interested. Interest is the keynote of effective occupational therapy treatment. While the tendency in military hospitals has been to use industrial activities because of their useful and masculine character, the fact should not be overlooked that the arts and crafts have

been practiced by great painters, architects, jewelers, and composers and are not considered effeminate occupations. The civilian hospital environment, of necessity, limits to a considerable extent the type of occupations which can be used. The problem is rather to interpret the treatment to the individual patient, so that he appreciates the reason for the activity used. Due account must be taken of the reactions of reluctance which the patient may show because of weakness and lassitude or because of an unspoken fear that his normal level of accomplishment may not be regained. The range of human interests is very wide; therefore, the tools of occupational therapy should be as varied as possible and should be adapted to the needs of the individual patient.

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## OPHTHALMOLOGY

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### Anterior Chamber

**Metastatic Tumors**—A case of metastatic carcinoma of the anterior chamber is reported.<sup>1</sup> This tumor involved the root of the iris, the ciliary body, the choroid, and the sclera. The metastasis followed radical mastectomy a year before the onset of the ocular symptoms.

### Brucellosis

**Diagnosis and Treatment**—Brucellosis is often manifested by eye signs.<sup>2</sup> The agglutination test is negative in most chronic cases. The test is valuable alone, only when it gives positive results in dilutions of 1:80 or higher. A weakly positive intradermal reaction is of the

same significance as a strongly positive one but it indicates a lesser degree of sensitivity and acts as a guide to the proper dilution of the vaccine to be used if this type of therapy is indicated. The test is made with 0.1 cc. of heat-killed vaccine prepared from the abortus strain only, in a concentration of 2,000,000,000 organisms per cc. Brucellergin (a filtrate of the three strains) is less sensitive as an antigen. The reaction is read at the end of four days. In acute cases, *sulfadiazine* or *sulfathiazole* are not curative but helpful. If remissions occur, vaccine should be used to build up adequate resistance.

### Conjunctiva

**Conjunctivitis in the East—Treatment**—Regular yearly epidemics of infective ophthalmias occur in Iraq, Palestine, and Egypt between May and December.<sup>3</sup> These cases are treated with *silver, expression, and copper stick*. Much blindness can be prevented by the routine use of *sulfonamides* in trachoma. Keratomalacia due to vitamin A deficiency is seen in Karachi, British India, and is successfully treated by shark liver oil. The chief evidence of leprosy in the eye is the presence on the conjunctiva of nodules which extend into the cornea and are associated with iritis and iridocyclitis. For this condition intramuscular injections of chaulmoogra oil are given routinely. Epidemics of keratoconjunctivitis in rice-eating countries are attributed to lowered resistance to virus infections due to a vitamin B complex deficiency. Severe cases of mucopurulent conjunctivitis are treated by the administration of M.B. 693 tablets internally. *Sulfacetamide* in drop or ointment form is slightly less irritating than sulfanilamide paste which consists of sulfanilamide powder, 20 per cent; cod liver oil, 40 per cent;

paraffin molle, 40 per cent. Vitamin B complex (yeast tablets) or riboflavin by mouth or injection is of assistance in the treatment of epidemic punctate keratitis.

**Gonococcal**—A case is reported<sup>4</sup> in which gonococcal conjunctivitis did not respond to sulfathiazole administered locally and by mouth but did respond promptly to *penicillin*. The penicillin was administered by the continuous intravenous method, 120,000 units in 2000 cc. of normal saline each day for two days and by the instillation of one drop of a solution of 1000 units per cc. every hour for twelve days. The condition improved within fifteen hours; cultures became negative by the third day. There was no corneal involvement and no recurrence.

**Gonorrheal**—A case of gonorrheal ophthalmia confirmed by smear and culture in a male, twenty-two years of age, is described by Town.<sup>5</sup> *Penicillin* was administered intramuscularly 20,000 units every two and one-half hours the first day until 140,000 units had been given; 200,000 the next day; 140,000 units the third day, *i. e.*, a total of 480,000 units. On the fourth day the eye became normal. No local antiseptic treatment was given but *atropine* was instilled daily.

**INTRAOCULARLY**—Seelig<sup>6</sup> reported a case of gonorrheal ophthalmia of fifteen days' duration complicated by ulceration of the cornea which was arrested by intraocular injections of *penicillin*. A course of *sulfathiazole* and 200,000 units of penicillin had been administered routinely. To begin with, 0.25 cc. (1250 units) of penicillin was injected subconjunctivally (with 0.06 cc. [1 minim] of 5 per cent procaine hydrochloride). This was repeated every fourth day for twelve days. At the same time, 0.18 cc. (3 minims) of a solution containing

500 units of penicillin per cc. was instilled every half hour as a "corneal bath" for two weeks. The infection cleared up and the two corneal ulcers healed after treatment with *trichloroacetic acid* and *atropine* so that 20/20 vision was obtained.

**Self-Inflicted**—Two cases of self-inflicted conjunctivitis are reported.<sup>7</sup> The most important diagnostic points in this type of conjunctivitis are: Edema of the lower conjunctiva as contrasted with a normal appearing upper conjunctiva; a necrotic area in the conjunctiva; scanty discharge; epiphora, and unusually rapid healing of the conjunctivitis.

**Ultraviolet Rays**—It is pointed out that ultraviolet lamps used for disinfecting purposes in hospital nurseries, hospital wards, and operating rooms may cause conjunctivitis.<sup>8</sup> Rays may be reflected from the lamp's reflector or from walls or floors for a period of minutes or hours. Because the intensity of radiation is inversely proportional to the square of the distance between the point of the source and the irradiated surface, significant dosages of reflected rays can be avoided by controlling the distance over which the reflected light must travel and by directing all reflected and direct rays toward a ceiling of soft finish.

**Pterygium—Treatment**—A modification and extension of the McReynolds operation for pterygium is described by Staz.<sup>9</sup> He suggests: Subconjunctival injection of novocaine and adrenalin into the lower fornix as well as at the site of the pterygium; prevention of overlapping of the conjunctiva of the upper limbus after transplantation of the pterygium; formation of a conjunctival flap to cover the raw scleral area and to lie along the limbus without encroaching on the cornea, to provide a vertical barrier to the recurrence of growth of horizontal vessels toward the cornea.

## Cornea

**Burns — Chemical**—An improved method of treatment of chemical burns of the eye is recommended by Oaks.<sup>10</sup> It is the procedure advocated by Pichler (Ztschr. f. Augenh., April, 1910) and by Middleton,<sup>11</sup> who performed repeated paracentesis of the anterior chamber. Paracentesis and drainage liberate aqueous which is loaded with the chemical. This procedure is particularly effective if performed in the first hour or two after injury. It should be a standard procedure for every severe or even moderate burn of the cornea accompanied by tissue destruction or haziness of the cornea.

In cases of burns by lime and lye, in which the cornea becomes white almost immediately, drainage of the anterior chamber should be instituted as soon as possible and repeated twice a day for several days, then once a day for three to five days longer.

**Dystrophy — Classification**—Von der Heydt<sup>11</sup> approves of Bueckler's classification (1938) of corneal dystrophies.

Fleischer's type, "broekelige," is a granular-disk form which begins as early as the fifth year and progresses until the thirtieth or fortieth year. Dystrophic changes occur within a central disciform area with a clear marginal border. The lesions resemble dried bread crumbs; the opacities are situated in the areas of the interlamellar cement substance. The epithelium is rarely involved. This is the most common type of hereditary dystrophy.

The Haab-Dimmer type of reticular dystrophy, "gittrige," is a lattice-form composed of irregular double-contoured superficial glassy lines usually split at their ends. In some early cases there is relative sparing of the pupillary area.

The Groenouw type of macular dystrophy, "fleckige-knotchen formige," consists of spotted, sometimes nodular, lesions beginning early in the second decade as diffuse spotted, rounded superficial and deep cloudings, extending to the limbus. As they increase in number and density, they may become elevated and nodular and lead to blindness.

Fuchs' epithelial dystrophy is a chronic edema of the central part of the cornea. In old cases of Fuchs' dystrophy and in glaucoma, the epithelium develops a chronic degenerative vacuole formation which differs from Groenouw's in that the lesions are fewer and the vascularization, which is present, surrounds the nodules but does not invade them.

Keratoconus is considered a corneal dystrophy due to a congenitally weak central stroma.

**Erosion—Recurrent—Treatment—** Recurrent erosion of the cornea usually follows even slight injury or abrasion of the cornea.<sup>12</sup> The recurrence is accompanied by sudden onset of pain and tearing with no obvious cause. Chandler suggests a clinical division of the condition into two types: the less common macroform and the more common microform. In the former, the corneal lesion is relatively large, the symptoms are prolonged and severe, and attacks recur at long intervals. In the latter the lesion is small (1 to 2 mm.), it can be seen with a +4.00 D. lens in the ophthalmoscope, and the symptoms are mild but the attacks recur frequently.

The microform is treated by introduction of 10 per cent **boric acid ointment** into the conjunctival sac at bedtime. The macroform is treated by the removal of all loose epithelium, followed by scraping and chemical cauterization of the denuded area.

**Insensitivity—Diagnosis—**According to Miller,<sup>13</sup> corneal anesthesia is

practically pathognomonic of hysteria. Out of a series of fifty cases of hysteria, forty-seven had bilateral corneal anesthesia.

**Keratitis — Interstitial — Nonspecific—Associated with Labyrinthine Disturbance—**Four cases of nonsyphilitic interstitial keratitis associated with vestibuloauditory symptoms are described by Cogan.<sup>14</sup> The interstitial keratitis was accompanied by vertigo, tinnitus, the nerve type of deafness and absence of labyrinthine function. The condition occurred in three young females and one male. The course of the disease is chronic and its cause is unknown. Syphilis, tuberculosis, mumps, influenza, and herpes zoster were excluded in this series of cases.

**Keratoconjunctivitis—Epidemic—**The administration of **convalescent serum** during the first few days of the disease is recommended for the treatment of keratoconjunctivitis.<sup>15</sup> The serum is difficult to obtain. Maumenee and his associates conclude that herpes simplex virus can produce a keratoconjunctivitis clinically almost identical with the epidemic form. Although the clinical picture and the cross immunologic reactions of the two viruses are similar, they are considered separate entities but are probably of the same genus. Intracellular inclusion bodies caused by the "E.K." virus were demonstrated experimentally for the first time. Treatment with **methylene blue** for herpes and epidemic keratoconjunctivitis is valuable in the early stages of these diseases. Removal of corneal epithelium by **iodine** or by **trichloroacetic acid** is effective in herpetic keratitis except in cases in which the virus also is present in the conjunctiva.

**Epidemic — Treatment —**Braley<sup>16</sup> indicates that as in trachoma, pannus must be present so in epidemic kerato-

conjunctivitis subepithelial infiltration of the cornea must be present before a clinical diagnosis can be established. Because the antibody titer can be found only long after the disease has run its course, the development of virus antibodies as a basis for diagnosis is of no value in making early diagnosis. The diagnosis is presumptive until corneal opacities develop. There are three stages: Edema and a foreign body sensation; follicular conjunctivitis, pseudomembrane formation and lymphadenopathy associated with symptoms of involvement of the upper respiratory tract; and retrogression of the conjunctivitis and the development of corneal opacities.

Sulfonamide, *penicillin* and *tyrothricin* are ineffective but intravenous convalescent *plasma* or *serum*, administered before the fifth day of the disease is most useful. In this series of cases, corneal opacities developed in all patients who were treated symptomatically, but in only one third of those patients who were treated with convalescent plasma.

**Transplant — Trephine** — A simple technic for corneal transplantation is suggested by Green.<sup>17</sup> It is performed in the following manner: Outline the area to be grafted with a 4.1 mm. trephine blade and stain with fluorescein. Insert an intracorneal stitch in a pattern outside the circle outlined by the trephine and place it so that when tightened it makes a cross which covers the graft. Insert a 4 mm. blade into an automatic trephine and cut a trephine button from the donor's cornea. Then substitute a 4.1 mm. blade and trephine the recipient cornea within the circle previously outlined with fluorescein. Insert the graft into the defect, and draw the sutures tightly and tie. The slight swelling which follows produces close

contact between the graft and tissues of the host.

**Ulcers**—Corneal ulceration may result from all kinds of bacteria, especially when the resistance of the cornea is reduced by previous general disease or exposed to occupational trauma.<sup>18</sup> Ulcers may be complicated by loss of vitreous, loss of lens, expulsive hemorrhage, and sympathetic ophthalmia.

**Treatment** — Routine first-aid treatment of eye injuries in the Edinburgh mines consists of the use of 10 per cent solution of albucid and 1 per cent optochin ointment. If conjunctivitis is present, it is treated; if dacryocystitis is present, *Toti's operation* or blocking of the lacrimal puncta is performed. To arrest infection, *sera*, *vaccine*, *iontophoresis* with *optochin*, the use of *extracts or lysates* of the lacrimal glands, *chemotherapy*, *caustics*, *radiotherapy* and surgical procedures may be used. *Sulfonamides* yield good results. Subconjunctival injections of *prontosil* in  $\frac{1}{2}$  cc. doses cure *ulcus serpens*. *Ultra-violet irradiation* of the ulcer for thirty seconds followed by irradiation for twenty to fifty seconds for three to five sittings yields good results. *Albucid* (30 per cent solution), *iodine*, *phenol*, 20 per cent *zinc sulfate*, or 0.3 per cent *zinc sulfate* by iontophoresis, thermocautery, paracentesis, fistulization, conjunctival flaps, heat and artificial fever therapy are all useful. Ulcers produced by Morax-Axenfeld diplobacillus respond to *zinc sulfate*, mycotic ulcers to *cautery* and scraping. For ring abscess, *parenteral protein therapy* is indicated. Herpetic ulcers respond to *iodine* and *scrapings*. Keratitis disciformis responds to *zinc iontophoresis*, *iodides*, *heat* and subconjunctival *saline injections*; Mooren's ulcer to local *cod liver ointment* or subconjunctival *injections* of *cya-*

*nide*. The use of 50 to 100,000 units of *vitamin A daily* is advocated as well as a solution containing *sulfonamides*, *atropine*, and a local anesthetic. Henley obtained good results in bacterial ulcers by the use of *x-rays*.

Evans<sup>19</sup> discusses the modern treatment of corneal ulcer. He points out that not only local but also general treatment is necessary. Local treatment includes *rest* (obtained by a firm bandage), *oily drops* or ointments,  $\frac{1}{2}$  to 1 per cent *cocaine* for relief of pain,  $\frac{1}{2}$  to 1 per cent *atropine* in cases which present circumcorneal injection or iritis, and *goggles* or *tarsorrhaphy* in neurotrophic and anesthetic ulcers of the cornea to prevent breaking down of the lesions. General treatment consists of proper diet and vitamins.

**Wounds—Repair Sutures**—The relative merits of corneal suture and conjunctival flaps used in the repair of perforating corneal wounds are discussed by Crawford.<sup>20</sup> His conclusions are based on a series of thirty-four cases in which corneal sutures were used and thirty-four in which a conjunctival flap was used. He found that corneal sutures yield better results than conjunctival flaps. With corneal sutures, the wound edges are more firmly closed, the period of healing is shorter, scarring is minimal, and secondary infection is rarer. Suturing is the method of choice except when the edges of the wound are ragged or edematous or there is loss of corneal substance.

### Dark Adaptation—Testing

#### Visual Function — Stimulation —

*Strychnine*—The use of a new method of testing dark adaptation based on Purkinje's phenomenon is reported by Kravkov.<sup>21</sup> He points out that visual function may be stimulated by strychnine, 0.7 mg. by mouth or 1 cc. of a

1:1000 solution subcutaneously. Strychnine has a stimulating effect on the discriminative power of the eye and the effect of the dose by mouth persists for about twenty-four hours. Benzedrine, 0.02 gm., had a deleterious effect on rod vision.

### Drugs

#### Cycloplegic—Dibutoline Sulfate—

A new mydriatic and cycloplegic drug—for use in cases of hypersensitivity or idiosyncrasy to atropine and its derivatives is presented by Swan and White.<sup>22</sup> It is a carbamic acid ester of the choline type chemically related to atropine. It produces paresis of smooth muscles innervated by the parasympathetic nervous system causing paralysis of the sphincter of the iris and the ciliary muscles but not of the dilator fibers of the iris. Its action may be enhanced by combination with epinephrine. A solution of 5 per cent dibutoline in distilled water has a pH of 6.5. The duration of its effect is comparable to that of homatropine but it is more potent. It also has an antiseptic action.

**Digitalis — Intoxication — Visual Symptoms**—Six cases of intoxication by digitalis are described by Carroll.<sup>23</sup> The patients complained that objects appeared white as if covered with snow. They had positive color scotomas and other visual hallucinations but the visual acuity and fields were not affected. The visual disturbances disappeared in from three to seven days after discontinuance of the drug. There were no objective findings.

The visual symptoms of digitalis intoxication are not well known. The general symptoms which are central in origin are well known. They comprise anorexia, nausea, vomiting and diarrhea, slowing of the heart rate, depression or



excitement, headache, impairment of memory, confusion, or delirium.

**Penicillin**—Bellows<sup>24</sup> states that penicillin is superior to the sulfonamides. Its effect is more potent on the staphylococcus and on other sulfonamide-resistant organisms and its bacteriostatic action is not inhibited by secretion or autolytic products. Moreover, penicillin has no adverse effect on regeneration of corneal epithelium. When given intravenously, penicillin reaches the eyeball within fifteen minutes. Its concentration in various tissues of the eye in descending order is: Extraocular muscles, conjunctiva, sclera, chorioretinal tissues and aqueous humor with only a trace in the cornea and vitreous and none in the lens. It has great penetrability when applied locally, producing a much higher concentration in the conjunctiva, sclera, iris, and aqueous humor than when given intravenously even in massive doses. However, for infections of the posterior segment, parenteral administration is necessary. Before treatment with penicillin, it is advisable to determine the sensitivity or nonsensitivity to penicillin of the organisms involved by direct contact with penicillin in a test tube. If growth of the organism is not affected, treatment will be useless. Penicillin locally may be given as drops, corneal baths, or ointment. Subconjunctival injections are not necessary. The concentration of penicillin in solution or ointment is usually from 250 to 2500 units per cc. or per gm. To be effective, drops must be instilled hourly. For hypopyon ulcer, a corneal bath, using a Barkan plastic lens or eye contact cup, is best. For anterior segment infections, ointment is best in a simple ointment base (U.S.P.). For treatment of the eyelid margins and the skin of the eyelids, the vanishing type of stearate base is better. Toxic effects after parenteral adminis-

tration include fever, chills, thrombophlebitis, urticaria, headaches, flushing of the face, and pain in the muscles. Irritation following local application may result from impurity or from hypersensitiveness to the drug. Conditions which have been treated successfully with penicillin include acute and chronic infections of the eyelids, especially blepharitis, and of the conjunctiva and cornea, sclera (episcleritis) and lacrimal sac (dacryocystitis), caused by the staphylococcus, streptococcus, gonococcus, and pneumococcus. For gonorrheal ophthalmia, penicillin is superior to sulfonamides. Parenterally, penicillin was found ineffective in cases in which bacteriologic factors were difficult or impossible to determine and in inflammatory disease of the uvea, such as chronic uveitis, chronic exudative choroiditis, chronic iridocyclitis, and sympathetic ophthalmia.

**Activity**—The activity of penicillin in conjunction with drugs commonly used in ophthalmic practice is discussed by Cameron.<sup>25</sup> Its effect was tested in association with atropine, physostigmine, epinephrine, cocaine hydrochloride, decicain (amethocain hydrochloride), argyrol, and fluorescein on plates sown with staphylococcus H (Oxford). Cameron found that argyrol with water inhibited the growth of the test organism as much as argyrol with penicillin; none of the other drugs had any inhibitory action on the staphylococcus, and epinephrine inactivated the penicillin.

**Lamellae**—The use of lactose lamellae in the conjunctival fornix, each containing 100 units of calcium penicillin is recommended in preference to penicillin drops because they can be kept at room temperature for as long as two months without deterioration.<sup>26</sup>

**Method of Use**—It is reported that an experimentally induced ectogenous

infection of the vitreous caused by a penicillin-sensitive strain of staphylococcus aureus was not arrested by intravenous injections of penicillin.<sup>27</sup> Repeated subconjunctival injections did arrest the progress of infection in four out of ten rabbit eyes and only a single intravitreal injection of 500 Oxford units halted the progress of the infection in all eyes. Lower concentrations were only partially successful.

**Penetrability**—The penetrability of penicillin into the eye is discussed by Sallmann.<sup>28</sup> His findings were as follows: (1) With a solution of commercial sodium penicillin containing 5000 Oxford units of penicillin per cc., the highest concentration was obtained in the aqueous by iontophoresis and in the cornea, iris, and ciliary body by prolonged application of cotton packs. The lowest concentration in the aqueous was obtained by subconjunctival injection. (2) With a solution of 20,000 Oxford units of penicillin per cc., high concentration of penicillin was obtained in the cornea, iris, and ciliary body after the application of cotton-soaked packs and in the aqueous it was also higher than that obtained with the other methods tested. (3) Depletion of penicillin from the ocular tissues and aqueous was practically complete eight hours after iontophoresis with a solution of sodium penicillin containing 5000 Oxford units of penicillin per cc. and after application of cotton packs saturated with a solution containing 20,000 Oxford units per cc. (4) After topical administration, only traces of penicillin were present in the lens and vitreous.

**Sulfonamides**—In discussing the use of sulfonamides in ophthalmology, Hill<sup>29</sup> points out that in posterior segment infections, oral administration in adequate dosage and in anterior segment infections, topical applications alone or

combined with oral administration are indicated. Adequate concentration of sulfonamides (except sulfanilamide) can be obtained in the cornea and sclera only by using a wetting agent, such as aerosol O. S. (0.2 to 1 per cent). Sulfonamides are useful for treatment of the following conditions: Trachoma, inclusion blennorrhea, catarrhal conjunctivitis, actinomycosis, serpent ulcers, cellulitis of the eyelids and orbit, endophthalmitis, panophthalmitis, and occasionally sympathetic ophthalmia. Sulfonamides are effective in infections caused by the staphylococcus, influenza bacillus, colon bacillus, and the gonococcus.

### Eye

**Herpes Simplex — Malaria** — According to Chamberlain and Bronson,<sup>30</sup> the incidence of dendritic keratitis among a group of malaria patients was 1 in every 188 new patients and in a non-malarial group 1 in every 1100. Less than 1 per cent of the patients admitted for malaria developed herpetic keratitis. Local applications of sulfadiazine powder promoted rapid healing in five cases of dendritic keratitis.

**Herpes Zoster Ophthalmicus** — A case of total herpes zoster of the ophthalmic, maxillary, and mandibular divisions of the trigeminal nerve was associated with involvement of the geniculate ganglion and the vestibular portion of the eighth cranial nerve.<sup>31</sup> Herpes zoster ophthalmicus is rare; herpes zoster of the ophthalmic, maxillary, and mandibular divisions is much rarer. The author found optic neuritis in four out of six cases. Treatment comprises intramuscular injections of *posterior pituitary solution* (0.5 to 1 cc.) or of *sodium iodide* (10 cc. of a 20 per cent solution) repeated on the second, fourth, and seventh days (Sidlick); heavy doses of *vitamin B* complex and *vitamin E*;

*diphtheria antitoxin* (5000 units, every other day); injection of *convalescent serum* (200 to 400 cc.); *whole blood* (5 to 10 cc.) into the gluteal region every other day combined with *thiamine hydrochloride* (25 mg.) twice weekly for six injections; and *smallpox vaccine*. Postherpetic pain may be treated with roentgen *irradiation* of the gas-serian ganglion and pons, high voltage rays to the back in the region of the posterior nerve root, injection of alcohol, or section of the sensory posterior root and section of the spinothalamic tract.

#### Multiple Sclerosis — Symptoms —

The early ocular symptoms of multiple sclerosis are described by Veasey.<sup>32</sup> Pain on movement of the eyes, "blotchy" interrupted slow vision which changes from time to time with or without contraction of the visual fields, the presence of central or paracentral scotoma and retrobulbar tenderness are suggestive of the earlier stage of multiple sclerosis. Classical symptoms which usually develop at a later period confirm the diagnosis.

**Ophthalmia Neonatorum — Treatment**—According to Sorsby and Hoffa,<sup>33</sup> the results obtained with *sulfonamides* in ophthalmia neonatorum are as good as those obtained with penicillin. They treated eight cases by instillation of a solution of 500 Oxford units of *penicillin*, introducing one drop every hour the first day, and one drop every two hours subsequently. Only three of these cases were cured. They treated seven cases with a solution of 1000 units per cc., using the same method in three cases, instilling a drop every half hour the first day and every hour subsequently. Four of these seven cases were cured. In ten cases in which a solution of 1500 units per cc. was instilled every half hour the first day

and every hour subsequently, six cases were cured. In twenty-two cases in which a solution of 2500 units per cc. was used every half hour for the first three hours, then every hour for twenty-four hours and subsequently every two hours, cure was obtained in twenty-one cases within 100 hours. Out of these twenty-two patients, five were cases of ophthalmia neonatorum caused by the gonococcus, nine by the staphylococcus, three by staphylococci and bacilli, two by inclusion bodies, and two by neither bacteria nor inclusion bodies.

**Parasites — Mode of Entry**—Nettel<sup>34</sup> discusses onchocercosis and the paths of invasion of parasites into the eye. He points out that the microfilarias usually reach the eye through the skin of the eyelids by way of the palpebral conjunctiva.

**Survey—Preoperative**—A comparison of the various technics of cataract extraction and the importance of a preoperative survey of the patient are presented.<sup>35</sup> Patients whose foci of infection (in teeth or sinuses) were either untreated or inadequately treated or who had no demonstrable focus of infection presented a high incidence of postoperative iridocyclitis. However, patients whose foci of infection were adequately treated prior to the extracapsular extraction did not develop postoperative iridocyclitis so frequently as either the untreated and inadequately treated group or the group with no demonstrable focus of infection.

Hughes and Owens conclude from a series of extractions of 2086 uncomplicated senile cataracts that: (1) The amount of remains of lens capsule and cortex after extracapsular extraction is related to the development of postoperative iridocyclitis and secondary glaucoma; (2) loss of vitreous predisposes to detachment of the retina, vitreous

opacities, and iridocyclitis; (3) corneo-scleral sutures reduce the incidence of incomplete closure, prolapse of the iris, and the amount of astigmatism; (4) a round pupil decreases the incidence of vitreous loss; (5) diabetes predisposes to the development of severe anterior chamber hemorrhages, and (6) that syphilis and hypertension have no influence on the development of postoperative complications.

**Vitamin Deficiency**—A case of ariboflavinosis in which new corneal vessel formation was present around the whole circumference of the cornea in both eyes is reported.<sup>36</sup> This condition occurred in a man, forty-nine years of age, who had been eating fruit and green vegetables only once a week. It was relieved by 15 mg. of riboflavin daily. Emptying of the new vessels after administration of riboflavin is considered diagnostic and differential between ariboflavinosis, rosacea keratitis, and interstitial keratitis.

**Vitamins**—Hahn<sup>37</sup> considers the presence of vitamins essential to the normal functioning of the eye. The vitamins and the ocular tissues with the function of which they are concerned are as follows:

**Vitamin A**—For maintenance of intact epithelium in the cornea and for regeneration of visual purple in the retina; **vitamin B<sub>1</sub>** (thiamin)—for metabolism of nerve tissue, *e. g.*, reception and conduction of the visual stimulus; **vitamin B<sub>2</sub>** (riboflavin)—for respiration of the cornea and for light perception and conversion of light to visual stimuli in the retina; **vitamin C**—for secretion of intra-ocular fluid by the ciliary body and for metabolism and respiration of the crystalline lens; **vitamin E**—for reparative processes; **vitamin K**—for blood coagulation, and **vitamin P**—for maintenance of the walls of blood vessels.

### **Wernicke's Disease—Treatment—**

**THIAMIN**—Wernicke's disease (encephalitis hemorrhagica superioris) is attributed to thiamine chloride deficiency by Kravitz and Stockfisch.<sup>38</sup> It is a neuro-ophthalmologic disease characterized by clouding of consciousness, varying ophthalmoplegias, and ataxia. Many cases of oculomotor paralyses may be a symptom of this disease rather than a "stroke" or "vascular sclerosis." The authors report three cases in which a history of alcoholism was absent but dietary deficiency was present. Cures were obtained by high vitamin diet, vitamin B<sub>1</sub>, and large doses of vitamin B complex.

### **Wounds — Perforating — TREATMENT—**

**Penicillin**—The use of penicillin is advocated for the treatment of infected perforating ocular injuries and for uveitis.<sup>39</sup> Scobee does not recommend subconjunctival injections of penicillin but penicillin eye drops combined with penicillin intravenously. Drops are given in the strength of from 250 to 500 units of penicillin per cc. of a 1.4 per cent saline solution. This strength of saline is preferred to the usual 0.9 per cent solution because it is isotonic with tears and penetrates more readily. The pH of the drops should be between 7 and 7.2. Zephiran may be added to the solution. The author recommends the injection of 25,000 units of penicillin in 0.9 per cent saline intravenously every twelve hours and the penicillin eye drops every four hours. Penicillin therapy is considered only as an adjunct in the treatment of uveitis. Improvement occurs within forty-eight to seventy-two hours after administration of penicillin but cure cannot be obtained by penicillin alone. Penicillin, 25,000 units in 0.9 per cent saline (2.5 cc.), is given every four hours totalling 150,000 units per day, for five to twelve days (1 per cent *atropine* is instilled in the eye three times daily).

Seventy-five per cent of cases improved but relapses occurred within five to seven days unless other accepted forms of therapy were also given.

### Eyeball

**Enucleation**—It is pointed out by Pfeiffer<sup>40</sup> that orbital contraction follows enucleation of the eye. The earlier in life the eye is removed, the smaller will be the orbit later in life. This finding is based on roentgenographic examination of thirty-one cases. Removal of the eye not only arrests the growth of the orbit but also leads to contraction and reduction of its capacity. Deformation of the orbit can be reduced by using an implant.

**Evisceration**—Gradle<sup>41</sup> discusses the relative merits of enucleation and evisceration. There are three major reasons for removal of an eye: Elimination of danger to sight or life; elimination of pain, and improvement of appearance. From an esthetic point of view, the operations in order of preference are: (1) Evisceration with implantation (of fat, glass, bone, or a gold ball) into the scleral capsule; (2) evisceration without a later implant; (3) enucleation with implantation of fat or a solid ball into the muscle cone, and (4) simple enucleation.

**Substitute Operations**—Enucleation and substitute operations are discussed by O'Brien.<sup>42</sup> The conjunctiva should always be preserved to avoid shortening of the *cul-de-sac*. In enucleation without implant, the recti muscles and Tenon's capsule should be brought together by a purse-string suture. An intrascleral implant affords the best cosmetic result. After the cornea is excised, it is advisable to remove a small triangular area of sclera, from above and below, to permit more accurate coaptation of the scleral edges over the implant. Detachment of the optic nerve from the sclera in-

creases the motion of the sclera. The implant should be neither too large nor too small (a bone sphere is not recommended). The fascia bulbi and conjunctiva should be sutured horizontally.

**Foreign Bodies—Intraocular—LOCALIZATION**—In discussing the localization of foreign bodies of low radio opacity in the eye, McGrigor<sup>43</sup> states that radiographs of the orbital region may mask the presence of fragments or foreign bodies of equal or lesser density than the superimposed bony structures. Localization and identification may be obstructed by distortion of the normal anatomic relationship of the eyeball by edema, hemorrhage, and laceration, multiplicity and different size of splinters of varying opacity. Moreover, light alloys, pyrex, and plastic foreign bodies have a low radio opacity. Foreign bodies in the anterior chamber can be revealed by a "bone-free" dental film or by Belot's projection method; in other parts of the eyeball—by an ordinary anteroposterior view with a small cone and a short exposure to obviate movement, a fine focus tube and short focus film distance, to blur the occipital bone. Stone and bakelite are not radio-opaque. The following technic is satisfactory for demonstrating lesser opaque foreign bodies: With extra speed blue brand or red seal dental film, use KV 78. mA 15, Dist. 50 cm., time 1½ sec., and localize by any standard P. A. method.

**Foreign Body—Intraocular—LOCALIZATION**—According to Macmillan,<sup>48</sup> x-ray localization is not necessary if a foreign body is visible in the anterior or posterior part of the eye or if a perforating wound of the cornea, traumatic cataract, or hole in the iris is present. However, if no response is obtained on repeated application of the magnet or if the foreign body is not metallic, x-ray examination is necessary and localization

is important. Sweet's localizer is preferred. It is accurate within 1 mm. and reveals the size and position of the foreign body in three planes. If this localizer is unavailable, radiograms should be made in two or more planes using a fixed marker applied to the conjunctiva or eyelid. Out of a series of 100 cases of foreign bodies in the eyeball x-rays were not used in 15 cases; the magnet was successfully used for foreign body extraction in 30 cases; and the Sweet localizer was employed in 69 cases. In 1 case, the x-ray was negative, but a foreign body was removed with the magnet. In 3 cases, a foreign body was localized outside the eyeball but the magnet extracted it from within it. In 7 cases, the foreign body was "nonmagnetic." Enucleation was done in 2 of these cases. Out of this series of 100 cases, 20 required enucleation.

**Glaucoma—Absolute—SCLEROTOMY**—A procedure for performing a modified technic of the trapdoor operation for absolute glaucoma is as follows:<sup>44</sup>

After incising the conjunctiva 8 mm. from the limbus, it is dissected toward the limbus; at a point 6 mm. above the limbus a scleral cut is made, 4 mm. in length, at 12 o'clock or at some other selected area. A cut (2 to 3 mm.) is made with scissors at each side of the scleral incision toward the cornea at an angle of 90 degrees. Black uveal tissue prolapses. A spatula is inserted through the trapdoor toward the anterior chamber, allowing escape of aqueous. The conjunctival wound is closed by a continuous silk suture. A double sclerotomy may be performed if the tension is very high and the eye painful. Most operations for glaucoma are limited to the corneoscleral margin. Herbert originally made his sclerotomy 1.5 mm. from the limbus; later 2, 3, and 4 mm. from it. Lehrfeld advocates placing the opening 4 to 8 mm. from the limbus, corresponding to the location of the ciliary body and beyond it. He explains that the trapdoor is not a fistulous opening; it serves as a wick. It is closed with a layer of uveal tissue, which acts like spongy weatherstripping for interchange of fluids.

**Cyclodiathermy**—It is pointed out that there are two types of diathermic treatment which may be applied to the ciliary region; the surface coagulation and diathermy puncture.<sup>45</sup>

For surface coagulation, between fifteen and twenty applications should be made with a very fine, short needle, using very little current, enough just to produce coagulation on the surface of the sclera. Cyclodiathermy punctures are placed over an area beginning from 2.5 to 3 mm. from the limbus to the ora serrata—on the nasal side, somewhat farther than the insertion of the medial rectus; inferiorly just beyond the insertion of the inferior rectus; the same distance on the lateral side and on the upper part of the eyeball not quite so far as the insertion of the superior rectus. The coagulation needle should be left in the sclera a little longer than one second. Somewhat more than one third of the inferior circumference is usually treated at one time. A good rule to follow in determining the number of punctures is as follows: The number of mm. of mercury of tension plus thirty equals the number of punctures required (but no more than eighty punctures should be made).

Cyclodiathermy puncture was performed in sixteen cases of chronic glaucoma. The method is considered harmless because no complications developed in any case. Not only the tension but also the general course of the disease was improved, the tension in most cases remaining reduced for a good period of time. For glaucoma simplex cyclodiathermy has some advantages over other operations. It is effective in all types of glaucoma; opacities of the lens do not develop. It is not followed by rapid deterioration of vision, such as may occur from some other surgical procedures and it is useful in all stages of chronic simple glaucoma. Cyclodiathermy puncture is also effective in glaucoma of the Negro.

**Primary**—ASSOCIATED WITH CATARACT—Guyton<sup>46</sup> discusses the choice of operation in primary glaucoma associated with cataracts. He studied a series of forty-four cases of chronic nonconges-

tive, congestive, and acute congestive glaucoma associated with cataract. In noncongestive glaucoma which does not respond to miotics, anterior fistulizing operations and deferred cataract extraction is advised; if the tension is controlled by miotics, combined cataract extraction is recommended. In chronic congestive glaucoma, combined cataract extraction usually controls the tension. In acute congestive glaucoma with high tension, preliminary iridectomy with subsequent cataract extraction is best; if the tension is low, or the lens greatly swollen, combined extraction is best without preliminary iridectomy. For the cataract extraction, the incision should be made below the bleb if the tension is low; through the bleb if the tension is normal.

**Treatment** — **SURGICAL** — According to Goar and Potts,<sup>47</sup> early operation in acute glaucoma is recommended if miotics do not relieve the tension within a few hours. They advise iridectomy *ab externo* for simple glaucoma, for subacute glaucoma, and for the prodromal stage in which an acute attack may be anticipated at any time. Its advantages over filtering operations are that the anterior chamber is emptied slowly; no instrument enters the eye; the lens is not endangered; and if desired a wick of iris may be left in the wound.

**Ophthalmia Neonatorum** — **Treatment** — The relative merits of the **sulfonamides** in the treatment of ophthalmia neonatorum are discussed by Sorsby and Hoffa.<sup>49</sup> The choice of sulfonamides lies between sulfamezathine, sulfathiazole, and sulfadiazine. Gonococcal ophthalmia was more successfully treated within a three-day period with sulfa-pyridine, sulfamezathine, and sulfathiazole than other cases of ophthalmia neonatorum. In almost one fifth of the cases, treatment was required for more

than eight days, relapses occurred or the medication was not well tolerated. Sulfamezathine was well tolerated but a larger proportion of cases responded poorly to it. From 30 to 40 per cent of cases were cured within three days and over 80 per cent at the end of eight days.

**Prosthesis** — **"Explosion"** — According to Hayes,<sup>50</sup> there is a partial vacuum inside a glass eye. For this reason, when a glass eye breaks in the orbit, an "explosion" is heard due to the inrush of air into the cavity of the glass eye.

**Tumors** — Fry<sup>51</sup> discusses the management of epibulbar tumors which may be benign, potentially malignant, or malignant. Examples of benign tumors are granulomas, epithelial plaques, papillomas, lipomas, hemangiomas, lymphangiomas, and dermoids. Nevi may be pigmented or nonpigmented raised areas with slightly irregular surfaces. They are benign but when they increase in size, pigmentation or vascularity, they should be completely excised. Malignant papillomas are nonpigmented nodular tumors, usually situated at the limbus. Examples of malignant tumors are sarcomas, epitheliomas, and precancerous melanosis. Malignant tumors should be excised and irradiated. In precancerous melanosis, exenteration of the orbit may be necessary. Two cases are presented, one of which indicates that sarcoma of the limbus may remain localized for years without involving the cornea, extending intraocularly or metastasizing and the other case indicates that an epithelioma of the limbus may rapidly extend into the cornea.

**Wounds** — **Perforating** — **TREATMENT** — The findings in a series of 172 perforating ocular injuries are reported by Snell.<sup>52</sup> In each case an attempt was made to save the eye. The final visual acuity in these cases was 20/100 or better in 50 per cent; 20/200 or worse in

50 per cent; 30 per cent regained 20/40 or better with correction; about 25 per cent lost sight perception and enucleation was performed in all but three of these cases. It seems that injury to the lens adversely influences the prognosis for recovery of vision mainly on account of the possible development of purulent infection and posttraumatic uveitis. Purulent intraocular infection developed in 15 per cent of these cases. Corneal lacerations may require (1) no surgical interference, simply treatment with atropine and pressure bandage; (2) a conjunctival flap after débridement and iridectomy; (3) corneal sutures after débridement and iridectomy, or (4) corneal sutures, conjunctival flap, débridement and iridectomy. One method of repair of perforating ocular injuries has no distinct advantage over another except in particular cases. Corneal wounds which coapt spontaneously without prolapse usually heal readily without operative treatment. Whenever surgical débridement of the wound is necessary, surgical repair is necessary. For prolapse of the iris, iridectomy should be done. Foreign bodies, pieces of cilia, and blood clots should be removed. Traumatic cataracts should be removed by lavage or piecemeal if it can be accomplished without aggravating hemorrhage, or prolapse. Whether to use corneal sutures or a conjunctival flap depends upon the degree of gaping of the wound. A conjunctival flap is useless if the wound gapes under the flap and a smaller scar will result if the wound edges are approximated with sutures. If the wound is irregular and the tissue macerated, sutures are impractical. If the lens is uninjured, insertion of sutures may traumatize it. If the wound is centrally situated and adherent, conjunctival flap would produce a leukoma greater than if the wound were closed with sutures.

Injection of air or saline into the anterior chamber may prevent anterior synechiae. Silk corneal sutures are removed in nine to twelve days. *Atropine*, *sulfathiazole*, or *sulfadiazine* and *artificial fever therapy* are usually indicated for cases complicated by traumatic cataract. If uveitis phacoanaphylactica occurs in the presence of traumatic cataract, treatment with *lens protein* and *staphylococcus toxin* should be tried.

### Eyelids

**Trachoma—Treatment**—Before sulfonamides were known, the following drugs were usually used: Copper stick, saturated solution of *quinine bisulfate* (2 per cent of the salt), *mercury perchloride*, *trachocid* (used as a paint 0.5 to 2 per cent solution in glycerine), and *bee venom* injected into the upper fornix and subconjunctivally at the limbus.

Sorsby<sup>53</sup> classifies trachoma into: Stage 1—active trachoma with follicle formation and sodden fornices; stage 2—moist tarsal conjunctiva without follicle formation and swelling of the fornix; stage 3—same as stage 2 but the conjunctiva is no longer moist and healing is taking place. Trachoma can be made noninfectious within three months and clinically cured in six months. The object in treatment is to convert stage 1 into stage 2. This may be accomplished by full doses of *sulfapyridine*, *sulfathiazole*, or *sulfamezathine* for ten days; mechanical expression of the follicles; after expression, painting with saturated solution of *quinine*, repeated three times daily for seven to fourteen days. Copper should be avoided during stage 1. Stage 3 requires no treatment, but *copper sulfate*, *zinc sulfate*, or *sulfacetamide* ointment may be used. *Atropine* is used if corneal lesions are present. Ulcers should be treated with



30 per cent *sulfacetamide* solution. Copper stick should be discarded; it has no place in the modern treatment of trachoma because it damages a moist eye and makes a dry eye moist.

### Fundus

**Ophthalmoscopy**—A number of conditions disclosed by ophthalmoscopy are reviewed.<sup>54</sup> In cases of closure of the central retinal artery in which recovery of vision occurs, spasm rather than plugging of the artery may be assumed. Closure of the central retinal vein may terminate in resolution, organization, scar tissue, or glaucoma. Painful glaucoma requires enucleation. In early toxemia of pregnancy spasm of one or more retinal arterioles with transitory obscuration of vision is the first sign. In papilledema increased translucency of the nerve fibers appears in the nasal part of the disk. In optic neuritis, loss of vision is the most outstanding symptom.

### Injuries

**War — Treatment** — The first aid treatment of war injuries of the eye is discussed by Tyrrell.<sup>55</sup> In cases of burns and scalds, the object is not only to prevent infection but also subsequent scarring. *Triple dye* is used to prevent infection of the eyelids; sterile liquid *paraffin* or *vaseline* to prevent symblepharon. After an explosion, irrigate the conjunctival sacs with any mild lotion, evert the upper eyelids to exclude the presence of dirt or debris on the tarsal conjunctiva and in the fornices. Then instill sterile liquid paraffin. Remove metallic bodies or glass promptly only if this can be done readily; if not, postpone until "shock" has been overcome. Do not attempt to remove grains of explosive. Instill *atropine* twice daily. For lime burns caused by falling ceilings irrigate with normal saline or 10

per cent glucose solution; instill atropine sulfate in castor oil or in watery solution and follow with sterile paraffin and bandage until the corneal epithelium is regenerated. In cases of penetrating wounds with retained foreign bodies remove the foreign body with a magnet if possible. If the foreign body protrudes from the wound, remove it at some later period. In all penetrating wounds, administer *sulfonamides*, such as sulfadiazine, or apply *penicillin* locally.

### Iris

**Rubeosis — Significance** — Rubeosis iridis is attributed to vascular and circulatory changes but especially to diabetes.<sup>56</sup> Three patients were observed with the syndrome of rubeosis iridis diabetica and two others without this syndrome in whom the findings were so similar that differential diagnosis was difficult. In both groups miotic therapy was ineffective and pain was intolerable. The new-formed vessels on the anterior surface of the iris were observed to lie in a layer of connective tissue attached to the anterior limiting layer. It is contended that rubeosis iridis represents a circulatory disturbance because it was associated with the development of hemorrhagic glaucoma. It is pointed out that rubeosis iridis is not a manifestation of an ocular syndrome seen only in diabetics.

### Lens

**Cataract — Complicated** — The Smith-Indian procedure for the extraction of many cases of complicated cataract is recommended by Green.<sup>57</sup> After corneal section extending from nine to three o'clock, iridectomy is performed, and pressure is applied with a hook at six o'clock about 2 mm. from the limbus and directed backward toward the ciliary body, the hook is then drawn across

the cornea from four to eight o'clock back and forth and the pressure is kept constant to keep the wound gaping. When the lens presents, pressure is continued with the hook indenting the cornea beneath it until the lens is received on the loop. It should be noted that pressure with the hook is not released until at least two thirds of the lens has emerged. One per cent atropine is instilled and the dressing is not disturbed for seven days postoperatively. Salicylates, 0.67 gm. (10 grains), two or three times a day are given during hospitalization for a week afterward. If a drawn-up pupil develops, an iridectomy may be made below at six o'clock after the eye completely heals.

**Electrical**—A case is reported by Adam and Klein<sup>58</sup> in which electrical cataract developed after 11,000 volts of electricity passed through the body by sparking contact with metal-rimmed spectacles. The visual disturbances developed six months after the accident. There were lens opacities and vacuoles in the lenses. A scalelike gray opacity developed in the anterior capsule of the left lens one and one-half years later. The process by which electrical cataract develops has not been explained.

**Etiology**—VITAMIN C—In a discussion of the relationship between vitamin C saturation and senile cataract, Rados<sup>59</sup> points out that the saturation test—the measurement of vitamin C output following intravenous injection of ascorbic acid—is the most accurate index of vitamin C deficiency. Out of 200 unselected patients who had cataracts, 135 patients (62.5 per cent) presented a saturation level of the body for vitamin C; 65 patients presented a low level of vitamin C excretion after intravenous administration of ascorbic acid. In thirty-five patients (18.5 per cent), the vitamin C deficiency was mild; in thirty-three pa-

tients (16.5 per cent), it was more marked and part of a general deficiency. He concludes that vitamin C deficiency is not a contributing factor in cataract formation and that transparency of the lens is not maintained by vitamin C saturation of the body. Patients with senile cataracts have a normal saturation level. In patients who have cataracts, the deficiency of vitamin C is the natural result of vitamin C deficiency of old age.

**Extraction**—COMPLICATIONS—*Pre-operative and Postoperative Treatment*—Frank<sup>60</sup> discusses not only the prevention but also the treatment of complications following operations on cataract and glaucoma.

Preoperatively dacryocystitis and conjunctivitis should be cleared up, increased tension reduced by miotics or by preliminary iridectomy, the blood pressure and urine checked, foci of infection eliminated, *calcium* given if clotting time is abnormal and a sedative, such as *nembutal* administered. Anesthesia is obtained by the O'Brien technic and by retrobulbar novocaine injection. For operation, Kalt's corneoscleral suture is recommended. If vitreous presents after corneal section, deliver the lens with a loop; if it prolapses after delivery of the lens, tie the sutures promptly and replace the pillars; if the lens is displaced deeply into the vitreous, remove it by a loop under illumination by a fluorescent lamp. Frank states that expulsive hemorrhage occurs in 1 to 5 per cent of cases of cataract extraction. Reduction of hypertension will reduce its incidence. Although Vail suggests immediate posterior sclerotomy for the treatment of this complication, enucleation is usually required.

Postoperative wound infection requires *cauterization*, *typhoid vaccine* intravenously, *hot compresses* and *sulfonamides* locally and internally. For

*uveitis* which develops at a later period *heat, atropine, calcium gluconate, salicylates*, and *foreign protein* are valuable. Prolapsed iris should be excised and the wound approximated and covered by a conjunctival flap. When soft cataracts are incised too freely, glaucoma may result although there is less tendency for this complication to develop if a through-and-through dissection is made. Operations performed for the relief of glaucoma may be complicated by iritis and hemorrhages into the anterior chamber, the vitreous, and retina.

**HYPHEMIA—Prevention**—The effect of ascorbic acid on the occurrence of hyphemia following cataract extraction has been studied by Mann and Pirie.<sup>61</sup> They found that prophylactic saturation with ascorbic acid did not decrease its incidence.

**INFECTION—Prophylaxis**—A preoperative study of the bacterial flora of 2508 cataractous eyes is reported by Dunnington and Khorazo.<sup>62</sup> The predominating organism was *Staphylococcus albus*, the next in frequency was *Staphylococcus aureus*. Most postoperative infections were caused by *Staphylococcus aureus* regardless of the type of operation. Postoperative infection occurred in 13 out of 730 cases in which no preoperative cultures were made but protein silver (25 per cent) was instilled before operation. No infections occurred in 663 cases in which *penicillin* ointment (1000 to 2000 Oxford units) or *sodium sulfathiazole* ointment (5 per cent) was used. No infections occurred in 104 cases which had had pathogenic organisms, but which were treated with penicillin or sulfathiazole preoperatively. The authors advocate preoperative cultures in every case in which cataract extraction is to be performed in order to institute proper preoperative prophylactic treatment.

### **Fibroplasia—Premature Infants—**

It is pointed out that retrolental fibroplasia develops in 12 per cent of all premature infants who weigh three pounds or less at birth.<sup>63</sup> In a series of 105 cases, the opaque retrolental fibroplastic tissue usually became less dense if no complications developed and searching nystagmus tended to abate or disappear with favorable development. Glaucoma occurred in 5 cases and *pilocarpine* was used daily to prevent development of glaucoma; in other cases, a weak mydriatic was used once a week to help prevent posterior synechia. The cause of the condition is not known. Sondermann attributed the glaucoma to overproduction of aqueous humor in relation to stricture of the vortex vein. He trephined the sclera over the ciliary body, relying upon the scar tissue repair of the lesion and the newly formed blood vessels along this tract to connect the circulation of the ciliary body with that of the episclera. The operation was successful. Similar operations, performed by Terry on nineteen infants, resulted in marked improvement in nine patients and relief of glaucoma without recurrence in another. There were no complications.

**Catmin**—Catmin lenses are reversed Galilean telescopic lenses which minify the image.<sup>64</sup> Although they are cosmetically undesirable and restrict the field of vision about 23 per cent, they are useful in unilateral aphakia and in cases in which contact lenses cannot be worn.

### **Muscles**

**Amblyopia ex Anopsia—Treatment**—According to Wells,<sup>65</sup> amblyopia ex anopsia can be improved by total occlusion of the better-seeing eye in most young children, many adolescents, and in a few adults during working hours. Alternating squints can be taught

to fuse by using a major amblyoscope and setting the image before the macula of each eye at the angle of squint. Anomalous correspondence in alternating divergent squint is rare. In convergent squint, it is common in cases associated with mechanical or structural anomaly. There is a high incidence of anomalous correspondence even in alternating squint with good visual acuity. The reflex from the light in the amblyoscope is never eccentric in one eye unless there is anomalous correspondence.

The major amblyoscope, the after-image, and the diplopia test are useful tests but normal correspondence may be found by one test and anomalous correspondence by another. It is important to realize that orthoptic training stimulates the sensorial apparatus in the cortex, not the muscles. In hyperopia by dissociating the convergence from the accommodation, patients with accommodative squint and hyperopia of not more than four diopters can be taught to keep their eyes straight without glasses. The author quotes Burian (1940) who states "the three factors causing the appearance of a periodic or manifest strabismus are: faulty mechanical conditions, abnormal innervational conditions, and a lack of fusion." The amount of squint is not a guide to the methods to be used to obtain fusion and stable binocular single vision or to the type of surgery to be used.

### Myasthenia Gravis

**Diagnosis—Treatment—**In reviewing myasthenia gravis and its ocular signs, Walsh<sup>66</sup> suggests that the ocular signs usually appear early in the course of the disease. Ptosis is the most constant sign; edema of the eyelids is a rare prodromal sign. Ocular movements may be limited but if pupillary abnormalities are present, the diagnosis of myasthenia

gravis is doubtful. *Prostigmine methylsulfate*, from 0.5 to 1.5 mg. per hypodermic syringe, is used for diagnosis and for emergencies. For treatment, *prostigmine bromide* is given orally in 15 mg. tablets three times a day in mild cases and 150 to 180 mg. in divided doses every three hours preferably combined with *ephedrine*, 0.25 gm., in severe cases. If large amounts of prostigmine are required, *atropine* is necessary to control cramps and diarrhea. Satisfactory results have been reported from thymectomy, x-ray therapy of the thymus, and the use of synthetic adrenal cortical extract.

### Nystagmus

**Etiology—**It is pointed out by Smith and Riesenman<sup>67</sup> that the origin of nystagmus may be vestibular, cerebellar, cerebral, upper cervical, or ocular. Among the unusual types are volitional nystagmus, which is horizontal, hysterical nystagmus, which is jerky and irregular instead of oscillatory, occupational nystagmus, which is horizontal and occurs in train dispatchers and miner's nystagmus, which requires from fifteen to twenty years for its development.

Nystagmus may result from lack of development of the macula, poor vision, dim illumination, or visual fatigue due to inability to fix with the macula.

### Optic Nerve

#### Amblyopia—Toxic—TREATMENT—

In a case of tobacco-alcohol amblyopia, occurring in a woman, normal vision and normal fields were regained following *vitamin B* therapy without decreasing her alcoholic intake or improving her diet.<sup>68</sup> After discontinuing thiamin, the amblyopia recurred but it was cured by using it again. It is suggested that in office and clinic practice, it is better to order a good diet supplemented by

the whole vitamin B complex as well as vitamin B<sub>1</sub> for treatment of this condition.

#### **Arachnoiditis — Optochiasmic —**

In a discussion of optochiasmic arachnoiditis, Hartmann<sup>69</sup> points out that arachnoiditis may be caused by infectious and toxic noxae. Pathologically, the condition is characterized by thickening of the arachnoid, adhesions, atrophy of the visual fibers, and the presence of circumscribed pockets of subarachnoid fluid. The findings suggestive of arachnoiditis are bilateral optic nerve atrophy, slight edema of the disk, concentric contraction, and sometimes a central scotoma. Syphilis may be an etiologic factor. Differentiation from toxic amblyopia with bilateral central defects (resulting from alcohol, tobacco, lead, thyroid and carbon disulfide) is made from the history and the fact that the central scotoma in arachnoiditis is larger, more irregular, and often associated with a peripheral contraction. Nonsurgical therapy consists of the use of semipenetrating *roentgen radiation*, intravenous injections of *sodium salicylate*, *sodium iodide*, *mercuric cyanide*, *methenamine* and *thiamin chloride*, and administration of *neurotropic vaccines* and *nonspecific proteins*. If improvement does not occur, prompt surgical intervention is indicated.

**Disk — Pigmentation** — Congenital pigmentation or melanosis of the optic disk is rare; complete pigmentation still rarer. Moehle<sup>70</sup> reports a case of complete congenital pigmentation of the optic disk in a male patient, sixty-five years of age. The pigmentation, which was brownish-black, was distributed over the entire disk and covered some of the retinal vessels. Vision was not affected.

**Papilledema—Diagnosis—ELECTRICAL SENSITIVITY OF EYE**—The value of electrical sensitivity of the eye was in-

vestigated by Kravkov and Mursin<sup>71</sup> in thirty-five cases of craniocerebral trauma in an attempt to utilize this method for differential diagnosis between choked disk and optic neuritis. They conclude that in (noninflammatory) papilledema the normal picture of adaptation changes of the electrical sensitivity of the eye is preserved and that in neuritis and retrobulbar neuritis, abnormal adaptation changes are characteristic.

**Tumor—Pigmented**—In two cases of aberrant fibers of the optic nerve, reported by Loewenstein,<sup>72</sup> ophthalmoscopic examination revealed the presence of a dark tumor of the optic nerve infiltrating the retina at one side. Histologic examination revealed that the retinal tissue was composed of nerve fibers which could be followed into the optic nerve. He considers this case to be a malignant degeneration of a pigmented nevus of the optic nerve. The second case was associated with hypertensive retinopathy and edematous swelling of the disk. A large "druse" bulged the fibers of the optic nerve over the end of Bruch's membrane and optic nerve fibers were pushed between the retina and the pigmented epithelium.

#### **Perimetry**

**Afterimages**—In Williamson's opinion,<sup>73</sup> the utilization of afterimages in perimetry is useful only for absolute field defects. In a patient who has a lesion of the central optic pathways, the afterimage may reveal a defect corresponding to the site and size of damage. He points out that one of the advantages is that the patient cannot look away from the fixation point because the afterimage moves with the shifting eye.

#### **Retina**

**Angioid Streaks**—According to Be-  
dell,<sup>74</sup> angioid streaks of the retina are

flat streaks or bands which form a peripapillary ring with radiating branches. They are not blood vessels. The streaks are flat but not uniform. They may be small, thin reddish lines or several times wider than the largest retinal vein and of a dark chocolate color. If the disease has existed for a long time, other changes in the fundus may appear, *e. g.*, aggregations of pigment, small or extensive retinal and choroidal hemorrhages in and about the macula which characteristically tend to become absorbed when fresh ones develop. The white spots along some of the streaks do not seem to be choroidal exudates. No new theory is presented to explain the etiology of angioid streaks.

**Detachment — Operation** — In discussing the basic principles of retinal detachment operations, Pischel<sup>75</sup> emphasizes the eyeball-shortening operation. There are several fundamental requirements for cure of retinal detachment: (1) The operation must result in the production of exudative choroiditis at the site where the tear will be when the retina is replaced; (2) the replaced retina must remain replaced long enough to permit the tear to be sealed by the exudate; (3) the subretinal fluid must be drained away and allowed to absorb, and (4) the hole or tear must be closed or walled off from the rest of the fundus by a solid line of watertight chorio-retinal adhesions. Pischel recommends partially penetrating coagulation with perforating diathermy and frequent fundus inspection during the course of the operation. If the detached retina becomes too small to fit the interior of the eye, an eyeball-shortening operation is indicated. Out of twelve eyeball-shortening operations, there were two cures and four improvements.

**Diabetes—Diagnosis**—According to Elwyn,<sup>76</sup> diabetic retinitis or retinopathy

is an entity characterized by small round and irregular hemorrhages, and sharply defined white exudates (due to deposits of cholesterol). The appearance is complicated by unrelated changes in the retinal vessels due to age, arteriosclerosis, contraction and obstruction. Some cases present large retinal hemorrhages which rupture into the vitreous. Newly formed vessels covered by a connective tissue layer and proliferation may occur in the retina and vitreous. Elwyn believes that the pathogenesis in diabetic retinitis is closely related to the continuous hyperglycemia which is responsible for the condition in the capillaries that result in hemorrhages.

**Injury—Roentgen Ray Glow**—It is pointed out that the extent of retinal damage (as well as the presence or absence of radiopaque foreign bodies) revealed by radiography and fluoroscopy is based upon the principle of recognition of a diffuse bluish-green glow by the intact retina when exposed to a direct beam of roentgen rays.<sup>77</sup> After remaining twenty minutes in a darkened room, the patient is placed facing the x-ray tube so that the field irradiated can be noted on the fluoroscopic screen. The patient's ability to recognize the retinal response to the roentgen beam is ascertained as well as his ability to describe the effects of irregular and repeated interruptions of the current. An intact retina was predicted in nine patients in whom the media prevented ophthalmoscopic examination and in fifteen patients whose retinas were destroyed, the response indicated this fact.

**Retinitis—Comparison of Diabetes and Hypertension**—Ballantyne<sup>78</sup> compares and contrasts the fundus changes in diabetes and hypertension. He states that the vascular changes, hemorrhages, and exudates common to both diseases present characteristic differences in form,

distribution and evolution of these components indicating that diabetic and hypertensive retinopathy are two separate clinical and pathologic entities. The lesions in the retinal vessels in diabetes tend to affect the venous retinal circulation with venous stasis, hemorrhages, exudates, congestion of the veins, microaneurysms of the capillaries and changes in the principal veins. Although aneurysms also are found in hypertension, especially after thrombosis of a branch of the central retinal vein, they are beyond the limits of the central area and are associated with obvious vascular changes and with grosser hemorrhages. In diabetic retinopathy, fatty deposits in the endothelium occur at the junctions and bifurcations of veins. Fatty droplets also occur in small retinal arteries in hypertension but in the middle and outer layers of the wall, not in the endothelium. With regard to the white punctate exudates common to both conditions, he points out that the exudates in diabetes coalesce and form larger waxy patches which are rounded, solid and hyaline. In hypertension the exudates are albuminoid, sometimes fibrinous and sometimes a combination of the two types.

According to Mann and Taylor,<sup>79</sup> early arteriolar changes are first evidenced by a widening and metallic appearance of the light reflex of the vessels. Later sheathing and a silver wire appearance develop. The veins become sclerosed at the arteriovenous crossings, the arterioles are more tortuous in the macular region and the entire arterial tree attenuated. Spasm may precede or accompany these signs. If changes are seen ophthalmoscopically, similar lesions may be assumed to be present in other organs. Hypertension primarily affects the arterioles. If retinopathy is absent, the prognosis of essential hypertension is

good. If hemorrhages or exudates appear, which indicate extensive vascular damage, the prognosis is unfavorable. Papilledema is the gravest sign. It occurs in malignant hypertension.

**Veins — Thickening** — It is pointed out that in the normal retina, the walls of the blood vessels are transparent so that only the blood column is seen.<sup>80</sup> Any thickening of the retinal veins indicates disease — diabetes, hypertension, retinal phlebitis, the vessels over a healed area of choroiditis. Rucker observed sheathing of only the retinal veins without visible disease of the retina in multiple sclerosis. Out of fifty cases of venous sheathing, multiple sclerosis was established in thirty-one instances; suspected in eleven cases and no evidence found in eight cases. The most common type of sheathing was thickening of the wall of the vein, less commonly there was a localized constriction of the caliber of the vein indicating that the thickening may have extended to the lumen.

### Tension

**Cocaine Instillation and Retrobulbar Injection**—In discussing the effects of retrobulbar anesthesia on ophthalmotonus, Campos<sup>81</sup> found that repeated instillation of a 5 per cent cocaine solution with adrenalin results in a marked drop in tension in 50 per cent of cases. This reduction in tension can be accentuated by retrobulbar injection of novocaine combined with adrenalin. The author also found that repeated instillations of cocaine, 5 per cent, with adrenalin reduces tension more than retrobulbar injections of 4 per cent novocaine solution with adrenalin. In most cases, reduction in tension appears within four minutes after the retrobulbar injection.

### Uvea

**Acute Iridocyclitis—Treatment**—In discussing the treatment of acute

iridocyclitis, Selinger<sup>82</sup> points out that the pupil must be fully dilated. This may be accomplished by the instillation of atropine every ten minutes for four doses followed by the introduction of powdered atropine in the lower fornix, and if the pupil fails to dilate after 45 minutes, by instillation of 1 drop of 10 per cent neosynephrin emulsion or solution. If these measures do not succeed, inject subconjunctivally a mixture of 2 drops each of 2 per cent cocaine solution, 1:1000 adrenalin and 1 or 2 per cent atropine solution two or three times a day until the eye is quiet. In cases of sensitivity to atropine, substitute any of the following:  $\frac{1}{4}$  to  $\frac{1}{2}$  per cent hyoscine hydrobromide solution,  $\frac{1}{2}$  per cent duboisin solution, 2 to 5 per cent homatropine hydrobromide, 1 per cent neosynephrine, 2 per cent cocaine solution, or 1 per cent ophthalmic epinephrine bitartrate ointment.

**Heat** may be obtained by means of hot moist compresses, a lamp, a hot water bag, or an electric pad.

Of foreign protein therapy, **typhoid-paratyphoid vaccine** intravenously is the most useful. It should be administered every second or third day for four to six doses in doses increasing from about twenty million to eighty million killed bacilli to elevate temperature to 103° F. A temperature-free interval of twenty-four hours between injections is desirable. Unpasteurized whole milk may be injected intramuscularly beginning with 10 cc. and increasing to 15 cc. if necessary. After typhoid or milk injection, the patient should be placed in bed and wrapped up in warm blankets. Fever and chills usually develop two to three hours after injection. Foreign protein therapy is contraindicated in old debilitated patients, in arteriosclerosis, hypertension, or heart disease and tuberculosis. For these patients use 10 cc.

of **lactogen** or **proteolac** intramuscularly every second day for six or more doses or **calcium gluconate**, 10 cc., intravenously or a half to a teaspoonful of the powder by mouth.

**Sodium salicylate** is useful—4 gm. (60 grains) twice a day or 2 to 3 gm. (30 to 40 grains) four to five times daily during the acute stage or 1.3 gm. (20 grains) three times daily combined with an equal amount of **sodium bicarbonate** throughout the course of the disease. Discontinue the salicylates if ringing in the ears develops. If **sulfonamides** are given, start with 2 gm. (30 grains) by mouth followed by 0.097 gm. (15 grains) every four hours until a blood concentration of 7 to 10 m. per cent is reached and maintained for a week. **Nembutal**, **sodium amytal**, and **codeine sulfate** may be useful.

**Conjunctivitis—Treatment—PENICILLIN**—The use of **penicillin** in the treatment of infections of the eye is discussed by Schnoor.<sup>83</sup> Three cases of acute iridocyclitis were treated successfully by intramuscular injection of 15,000 Oxford units every three hours for three days, and followed by sulfadiazine by mouth, 1 gm. every four hours and typhoid II antigen intravenously every other day in doses sufficient to produce a temperature of 103° to 104° F.

Penicillin eye drops (500 Oxford units per cc.) were instilled in twenty-eight cases of external infections of the eye, using 1 drop every hour for the first day and every two hours for the second day. After improvement resulted, it was used four times a day. Excellent results were obtained in 60 per cent of this series of twenty-eight cases.

**Uveitis—Etiology—TUBERCULOSIS**—Reese<sup>84</sup> discusses the participation of the eye in general diseases. Uveitis is caused by tuberculosis in 40 per cent and verifiable in 20 per cent of cases.



In 20 per cent a presumptive diagnosis is justifiable if based on (1) characteristic iris nodules and a general picture suggesting tuberculosis; (2) healed or active systemic tuberculosis with sensitivity to tuberculin or the presence of an ocular lesion suggesting tuberculosis without evidence of any other etiologic factor; (3) systemic tuberculosis or hypersensitivity to tuberculin with evidence of either syphilis or a focus of infection but with a chronic recurrent clinical course or with other lesions, suggesting tuberculosis without relationship of the ocular disease to a focus of infection or syphilis. Treatment consists of bacteriostasis, by general hygienic measures, repeated paracentesis of the anterior chamber, nonspecific protein therapy, beta radiation and reduction of hypersensitivity by tuberculin in doses insufficient to produce focal, local, or general reactions. About 50 per cent of cases of sarcoid present ocular lesions. Brucellosis can be established as a cause only in the acute stages, diagnosis being made by a high agglutination titer in the blood serum and isolation of the organism, but positive skin tests and intermittent low fever are presumptive indications of the disease. Toxoplasmosis in infants always presents bilateral, focal, usually multiple, choroiditis, especially at the macula, and, in advanced cases, detachment of the retina, granulation tissue formation in the vitreous resembling retinoblastoma or the remains of the vascular capsule of the lens. In all infants and children who have ocular symptoms associated with convulsions, hydrocephalus, and mental retardation, toxoplasmosis should be suspected.

**Penicillin**—A series of fifty-six cases of anterior and posterior nonspecific uveitis was treated with penicillin by intramuscular injections and eight additional cases of anterior uveitis were treated by

penicillin iontophoresis. It was found that only in acute anterior uveitis (iridocyclitis) was more marked improvement obtained during or after treatment than would be expected with the usually accepted forms of treatment (atropine, heat, and foreign protein).<sup>85</sup> It seems that penicillin-sensitive bacteria are not usually involved in the etiology of non-specific uveitis.

**Treatment**—A discussion of uveitis, its diagnosis, prognosis, and treatment and its relation to focal infections and allergy is presented by Gill.<sup>86</sup> Uveitis may be caused by syphilis, tuberculosis, trauma, foci of infection, food allergies, or vitamin deficiencies. Local treatment consists of the use of *atropine*, 2 per cent, with *neosynephrine* or *paredrine*, *massage* to break up synechiae, *hot compresses*, and *dionin*. General treatment consists of the routine administration of *foreign proteins*, *typhoid* (hypodermically in daily doses of 0.5 cc. or intravenously in doses of about 1 minim); *sodium salicylate*, 3 gm. (40 grains) in 4 ounces of water three times a day per rectum; removal of foci of infection; relief of constipation; vaccines prepared from streptococci found in the stools; antisyphilitic treatment and old tuberculin intradermally and chaulmoogra oil esters (in leprous uveitis); *skin testing* and *elimination diet* (in allergic uveitis); vitamins A and D (in deficiencies); *calcium* and desiccated *parathyroid gland*, 0.004 to 0.003 gm. ( $\frac{1}{16}$  to  $\frac{1}{20}$  grain) three times daily or parathyroid extract in 0.5 cc. doses hypodermically once a day (may be helpful in some cases) and desensitization by hypodermic administration of normal suspension of uveal pigment (with tricresol as a preservative). If the skin reaction to uveal pigment is positive, administer 0.25 cc. of the pigment suspension daily, increasing by 0.25 daily

until 2 cc. have been given (in sympathetic ophthalmia.) (If sulfonamides are used, discontinue all of the other internal medication.)

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## OTORHINOLARYNGOLOGY

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### GENERAL CONSIDERATIONS

**Vitamin Therapy**—Vitamin therapy in otolaryngology is discussed by C. C. Cody.<sup>1</sup> Recent investigations confirm the general rule of vitamin therapy, that a vitamin can relieve only those symptoms caused by its deficiency. The avitaminotic diseases are clinical entities with a definite pattern of symptoms and pathogenesis both in man and in laboratory animals.

Vitamin A has no effect on immunity. It is of no value in the treatment of infections unassociated with metaplasia of the mucosa due to nutritional deficiency. The benefiting of frequent and recurrent colds by the administration of vitamin A proves merely the existence of a deficiency in the diet. Vitamin A is indicated in certain types of chronic sinusitis in addition to the local treatment. Atrophic rhinitis may be a sequela of chronic sinusitis from avitaminosis.

The general etiologic factors for a clinical deficiency of the vitamin B group are a relatively low and highly variable vitamin content of the usual foods, rather meager storage facilities

for these vitamins in the human body and their rapid metabolism or excretion. Alkaline fluids rapidly destroy the vitamins of the B group. The methods of processing and preparing foods for the table affect their thiamine content.

The presenting otolaryngologic complaints associated with latent beriberi may be nasal discharge, sore throat, hoarseness, a lump or ball in the throat, difficulty in swallowing, tinnitus or impaired hearing. A nasal syndrome has been identified with thiamine deficiency. The presenting complaint is slight but frequent postnasal discharge. Mucus is expectorated at short intervals. Sneezing is occasional but does not occur in bouts. There is no headache. Young women are most often affected.

A pharyngeal syndrome has the presenting complaint of sore throat and occurs more frequently in the summer and autumn. The clinical picture of the enlarged arytenoids in thiamine deficiency and in tuberculosis of the larynx is somewhat analogous. Patients with globus hystericus who have edema of the arytenoids typical of thiamine deficiency are relieved of their symptoms

within five days by 30 mg. of *thiamine hydrochloride* a day.

The laryngeal syndrome producing voice changes present two clinical pictures: One occurs occasionally in the edentulous aged, usually in women, and the other extremely rare form is seen in infants. In the aged, the voice, although strong, rapidly tires on talking and has a peculiar sound as though the end of a syllable or word is split or fuzzy. Edema of the arytenoids is present, and the vocal cords are moist, though normal in color. On phonation, the edges of the vocal cords are brought together but cannot be held in close approximation and so are slightly separated. The vocal cords become dry and normally approximated and the voice clear after ten to fourteen days on 30 mg. of *thiamine chloride* a day.

Thiamine hydrochloride is effective for a few conditions in which the precise relationship to nutritional deficiencies is not at present clear. It affords protection against the toxic effects of roentgen rays. Clinical experience has confirmed the observation that thiamine hydrochloride has a synergistic action on thyroid.

That some persons are susceptible and others resistant to vitamin C deficiency is the only conclusion possible from the rather contradictory reports on human requirements for *ascorbic acid*. The conclusion that ascorbic acid benefits hay fever is in dispute. Some do improve. The symptoms of the group which showed no benefit were diagnosed as nasal allergy. But the improvement or cure in the other group indicated that vasomotor rhinitis may be an early symptom of early or subclinical scurvy. Nearly all of the latter group were found to be on diets containing little or no citrus fruits or fresh vegetables.

Vitamin D has a function in the metabolism of calcium and phosphorus in the maintenance of their normal ratio to each other.

The diagnostic methods are at present clinical examination and therapeutic tests; suitable laboratory tests for clinicians are hoped for in the future. The therapeutic action of the vitamins is precise and specific. Consequently, the otolaryngologist in prescribing vitamins should treat diseases and not symptoms.

**Hypometabolism**—Hypometabolism in the practice of otolaryngology is discussed by J. W. McLaurin,<sup>2</sup> who states that the less obvious etiologic factors are malnutrition, mental strain, worry, or sense of insecurity of life. Obesity is the classic sign which usually directs attention to hypothyroidism, but many thin persons who never have gained weight do so when started on a well-regulated course of *thyroid* treatment. Whereas somnolence, forgetfulness, and lack of concentration are signs of true myxedema; restlessness, nervousness, and insomnia are more apt to be observed with hypometabolism. Headache, low blood pressure, and general fatigue are frequent complaints of the patients. Other symptoms include blockage of the eustachian tubes, nasal obstruction, post-nasal drip and repeated colds, voice changes, and other vague pharyngeal and laryngeal complaints.

The clinical diagnosis can be substantiated by determinations of the basal metabolic rate. The diagnosis of hypometabolism in a young or mature adult does not present as difficult a problem as that of hypometabolism in a child.

The contraindications to *thyroid* medication may be listed as follows: Hyperthyroidism; diabetes mellitus; serious organic heart disease; persistent tachycardia; tuberculosis and extreme degrees of malnutrition. The author

urges that, as long as there are no contraindications, thyroid be given an adequate trial even though the basal metabolic rate is within normal limits.

The treatment consists in the administration of any form of the prepared gland or its active principle. It is well to fix on one brand and continue its use. One should begin with a small amount and increase the dose gradually until the symptoms for which it is given have disappeared. The amount of medication is strictly an individual problem. After freedom of symptoms, the dose can be decreased gradually and the therapy finally stopped, when the metabolism becomes normal.

**Facial Neuralgia**—Spasmodic facial neuralgia is the subject of an enlightening review by R. L. Glass.<sup>3</sup> According to Glass, fundamental in the diagnosis of pain in and about the face are: The pain path affected, its point of involvement, and the nature of the irritant.

The chief routes of pain from the general region of the face to the sensorium are:

1. Trigeminal nerve (brow, eyelids, nose, cheek, lips, chin, part of ear, nasal fossa, palate, anterior two-thirds of tongue).

2. Facial nerve (part of auditory canal and tympanic membrane through the nerve of Wrisberg).

3. Glossopharyngeal nerve (posterior one-third of tongue, tonsil, faucial pillars, soft palate, pharynx, eustachian tube, tympanic cavity, mastoid cells).

4. Vagus nerve (part of auricle and of external auditory meatus through the nerve of Arnold).

5. Small occipital nerve (part of pinna).

6. Great auricular nerve (part of auricle, angle of mandible).

7. The sympathetic.

A pain stimulus may be applied at different points along any one of these structures—peripheral nerve branch, ganglion, ganglionic or spinal root. Pain elaborated at the psychic level—so-called psychalgias, but better labeled as plain hysteria—also occurs, and at times is easily confused with an organic neuralgia.

The nature of the irritant, the lesion or the underlying pathological-physiological process, cannot be identified in numerous cases. This is because the essence of many neuralgias is obscure. However, a certain differential classification, necessary for proper treatment of the patient, can usually be made. To succeed in this, the clinician must heed certain points. Of these, the most important are: (1) Precise location of the pain; (2) character of the pain; (3) its mode of occurrences; (4) its relation to various external stimuli and to acts involving muscles of the face, jaw, tongue, and throat; (5) the patient's general behavior during the time of the pain; (6) specific features characteristic or highly suggestive of well-known clinical syndromes; and (7) associated neurological findings.

Of prime importance is precise location of the pain. In various entities, there is a difference in its quality or character, while the mode of occurrence varies, too. Of great value in diagnosis is the relation of the pain to external stimuli or to acts requiring contraction of the muscles of the face, jaw, tongue, or throat. The patient's general behavior during the attack of pain has valuable differential diagnostic weight. Specific features typical or highly suggestive of known clinical syndromes will aid in classification of the pain. In occasional cases, associated neurological findings are invaluable.

The neurological treatment of pain about the face is either specific or palliative. In the former, the lesion causing the pain is eradicated by a surgical procedure, such as removal of a tumor of the gasserian ganglion or of the cerebellopontine angle. Palliative treatment involves interruption of the route of the pain impulse to the sensorium.

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## OTOLOGY

**Allergy**—Nasal allergy for the practicing rhinologist is the subject of an enlightening presentation made by George E. Shambaugh, Jr.<sup>4</sup> Three phases are discussed: I. Pathologic and Theoretic Considerations; II. Methods of Diagnosis of Nasal Allergy; III. Treatment of Nasal Allergy.

I. While the nasal and sinus mucosa of some persons has the ability to recover spontaneously and completely from certain severe infections, there is an inability in others to throw off and recover from the very mildest type of low-grade infection, particularly when hyperplastic and polypoid changes are present in the ethmoid and other sinus regions. It has been only recently that we have begun to learn that there is an underlying allergy in these cases. At least 70 per cent of chronic sinus infections, and at least 90 per cent of chronic nasal infections can be shown to have an underlying allergic factor responsible for the chronicity.

The allergic reaction is believed to be an immune reaction, the result of the union of specific antibodies with the particular substance to which the person is allergic. We do not know what in the allergic individual makes him develop antibodies against substances which normally do not stimulate antibody production and the consequent

symptoms, except that heredity is an important factor. The pathology of the allergic reaction is seen in the positive skin test. The allergic reaction should be regarded as a defense reaction, or immune reaction, against an invader.

Nasal allergy in its early stages is a reversible reaction, so that after the hay fever season, the "waterlogged" nose usually returns entirely to normal. Long-standing allergy, when complicated by infection, results in irreversible hyperplastic and polypoid changes in the nasal and sinus mucosa.

The best therapeutic results will follow only when the infection and the allergy are treated simultaneously, and this can be accomplished best by the rhinologist who makes his own allergic studies.

II. Nasally, allergy is suspected on the basis of the patient's symptoms, the appearance of the nasal mucosa, and the finding of eosinophiles in the nasal smear. To find the offending allergy, the patient's history, the skin tests, the elimination diet, and the therapeutic test are employed. In the last analysis, the proof of an allergen depends upon the therapeutic test: Recovery from symptoms when the specific substance is removed, and recurrence of symptoms when the patient is again exposed to the substance. The skin tests must be regarded merely as an aid, and not as the sole means of diagnosis.

III. Sensitivity to house dust is a major factor in most of the nasal allergy encountered in rhinologic practice. Therapeutic response to injections of house dust extract is very satisfactory in the great majority of cases. The treatment of food allergens consists of removing the allergic foods from the diet. Injections of food extract have not proven satisfactory in the treatment of food allergies. While the allergic patient is

sensitive to a number of substances, one or two of these will be chiefly responsible for his symptoms. When these are removed, or he is treated for them, his symptoms will be relieved. As has already been stated, in order to restore the patient to "allergic balance," and to relieve his symptoms completely, the infections as well as the allergies must be recognized and treated.

**Ménière's Symptom Complex**—H. I. Lillie, B. T. Horton, and W. C. Thornell<sup>5</sup> discuss Ménière's symptom complex and report their observations on the hearing of patients treated with histamine. Their paper is based on twenty-five cases of Ménière's symptom complex in which histamine was administered.

Two and seventy-five hundredths milligrams of *histamine diphosphate* (one milligram of histamine base) was administered intravenously in *physiologic salt solution* (250 cc.), a 5 per cent solution of *dextrose* (250 cc.) or in a 0.8 per cent solution of *potassium chloride* at the rate of 20 to 60 drops per minute. The blood pressure and the pulse rate were checked frequently during the injection. Histamine was administered daily in this manner for three to six days. In conjunction with or following the injections, subcutaneous administration of histamine (a 1:10,000 solution of histamine base) was begun; at first the dose was 0.2 cc. but this was increased by 0.05 cc., twice daily, up to 1.0 cc. or until the optimal dose was reached. The patient was then instructed to continue with the daily injections of histamine and gradually taper off the dose according to the response of treatment. In several cases in which the symptoms were especially severe, intravenous injections were administered for many days. In many cases, histamine was administered intravenously during

the subcutaneous "desensitization," to abort an attack of vertigo.

Improvement in the deafness was noted in twelve cases; the greatest improvement was noted in the cases in which the histamine was administered intravenously in an 0.8 per cent solution of potassium chloride. Improvement in the tinnitus immediately following treatment was noted in fourteen cases and improvement in vertigo was noted in twenty-one cases. The authors concluded, despite the insufficient number of cases to warrant drawing definite conclusions, that in a goodly number of cases of Ménière's symptom complex in which histamine is administered, the hearing improves and there is considerable relief of tinnitus.

To overcome misconceptions regarding intravenous histamine therapy, the authors relate that the method of giving histamine intravenously in a 1:250,000 dilution is a simple procedure, and a large number of such injections have been given to patients with Ménière's symptom complex without untoward effects.

**Penicillin Therapy in Infectious Diseases of the Ear**—An interesting and valuable presentation on the use of penicillin in diseases of the ear was made by C. A. Swanson and D. C. Baker, Jr.<sup>6</sup> They told that infectious diseases of the ear can be effectively treated with *penicillin* because the anatomic structure of the ear permits the local administration of the drug and because the organisms causing most acute infections of the ear are usually in the group considered to be susceptible to the drug.

In acute otitis media, penicillin is administered by intramuscular injection. The amount of the drug necessary to combat the infection will vary according to its causative organism and severity.

Staphylococcic infections, as a rule, require a greater amount of penicillin than those due to streptococci. The drug should be continued after the patient has appeared to recover to avoid possible relapse.

When surgical intervention is done for acute mastoiditis, it can be supplemented by penicillin administered either by intramuscular injection or by local instillation into the mastoid cavity. Penicillin can be administered by continuous intravenous injection for the treatment of acute labyrinthitis. In special instances, chronic otitis media can be treated successfully by the local instillation of penicillin into the middle ear. The patient who has a chronic discharging ear caused by an organism susceptible to the drug and has a large perforation of the eardrum with no evidence of granulations or cholesteatoma is best suited for penicillin therapy. The pneumatic otoscope can be used to force the drug into the middle ear and the penicillin can be sealed into the ear by means of cotton impregnated with a bland ointment.

Penicillin has been employed with substantial benefit in many instances in which other forms of therapy had failed. It was possible either to avoid surgical intervention for acute mastoiditis or to use the drug as a supplement to surgery with significant help. When the drug is instilled into the mastoid cavity after operation, healing is prompt and the period of convalescence is shortened. According to Swanson and Baker, penicillin is the most powerful chemotherapeutic agent available to combat acute otitis media, acute mastoiditis, and their complications.

**Otosclerosis**—Eighty-five fenestration operations for otosclerosis represent the basis of a report by J. M. Smith.<sup>7</sup> Since the first series consisting of thirty-

two cases, fifty-three additional operations were performed, and in this latter group the results were more successful than in the first series. The improvement in the results dates back to the new location of the fistula. In the first eighteen operations of the total of eighty-five the fistula was made over the length of the external semicircular canal posterior to the ampullated end, with the head of the malleus removed and the incus in its normal position. In the rest of the series, sixty-seven in number, the fistula was moved forward over the dome of the vestibule anterior to the ampullated end of the horizontal semicircular canal, with the head of the malleus and the incus removed. The operation should be performed before serious impairment of nerve function takes place. If nerve function is lost, the operation will prove useless.

In the eighty-five operations there were no complications or mortality. It is Smith's belief that if the operation is successfully performed, it not only restores practical hearing, but also retards the progress of otosclerosis.

#### **Education of Deaf Children—**

C. E. Rankin<sup>8</sup> reviews the subject of education for children handicapped by deafness. In the main he describes the routine of the North Carolina School for the Deaf, the character of its student body, the criteria for admission, and other factors. Of interest to the otologist are the statistical aspects of the problem of child deafness. A recent survey made in the upper school, 156 unselected students furnishing reliable information, shows that 59, or 37.8 per cent, lost their hearing in early childhood, 12 of them after the age of six. Of this number, 24 owe their loss of hearing to spinal meningitis; in 22, 14.1 per cent, the cause of deafness being illnesses such as scarlet fever, typhoid



fever, and ear infections in later childhood. Seventy-five, or 48 per cent, of the 156 students were born deaf. Forty-one of these have one or more deaf sisters or brothers; 12 are children of deaf parents, and 18 are children of hearing parents having deaf relatives.

Physicians could render valuable service by ascertaining in early infancy whether or not deafness has been inherited by the offspring of deaf partners, or of hearing partners having deaf ancestors or relatives. We have had in school children of deaf parents who were themselves thought to be deaf, but were found to have normal hearing; they simply had no chance to make use of it. On the other hand, many deaf children are considered normal until they reach the age of two or three years. Much good could be done by putting children of deaf parents in such environments that they would not lose anything in the early training of hearing and of speech, and by preparing deaf children of hearing parents for school by means of lip reading.

Rankin urges that deaf or partially deaf children should be put into special schools as early as possible for rehabilitation training.

**Otitis Media—Chronic Suppurative Otitis Media**—An interesting and informative discussion of chronic suppurative otitis media has been presented by L. R. Boies.<sup>9</sup> In the author's personal experience, he has observed the development of chronic middle ear suppurative:

1. As the sequela of a severe infection causing necrotic change in some portion of the tympanum.

2. In acute otitis media in an ear in which the mucosa has remained hyperplastic.

3. As the result of the formation of a cholesteatoma from an ingrowth of

epithelium from Shrapnell's membrane without preexisting perforation or otitis media.

4. As a complication of ordinary acute otitis media in an ear with normal pneumatization.

The following definition of chronic suppurative otitis media is suggested: It is a continued suppuration from the middle ear following an acute necrotic otitis media or a primary suppuration in a middle ear with hyperplastic mucosa; uncommonly, it occurs following an invagination of epithelium from Shrapnell's membrane to form a cholesteatoma without preexisting perforation, or an ordinary otitis media in a previously normal middle ear.

In otology, cholesteatoma refers to an accumulation of horny and desquamated epidermis and cholestrin crystals. The cholestrin results from decomposition of organic matter out of contact with oxygen. The author prefers the use of "primary" and "secondary" to designate the two types of pseudocholesteatoma. The "primary" pseudocholesteatoma is the "genuine" type of Wittmaack. The "secondary" pseudocholesteatoma is the type commonly encountered in chronic suppurative otitis media.

It has been found helpful to use a classification of chronic suppurative otitis media suggested by Lillie. There are four types:

Type I is characterized by a thin mucoid discharge with little or no odor.

Type II is characterized by pathologic changes confined to the middle ear.

Type II has its most striking pathologic change in the attic although the conditions described in Types I and II may be associated. The odor of the discharge is foul. It may be scanty. The perforation is in Shrapnell's membrane or along the posterior margin of

the tympanic membrane. Cholesteatoma is usually present.

Type IV contains all cases in which there are signs of extension of the disease to the labyrinth, meninges, brain or facial nerve. Cholesteatoma is invariably present. Surgical intervention is positively indicated.

From the standpoint of diagnosis, the following facts merit consideration:

1. The character of the discharge may indicate at first examination the nature of the pathologic process.

2. Objective signs in the middle ear exclusive of the discharge are of considerable diagnostic value.

3. Hearing loss varies in degree according to the site and type of the pathology.

4. The fistula test should be performed in every case of chronic middle ear suppuration of Types III and IV.

5. Pain is an uncommon symptom in the ordinary case of chronic middle ear suppuration. Its presence is of serious import. It may mean that: (1) Tension has developed due to a stoppage of secretion (pus or cholesteatoma); or (2) the dura or sinus wall has been exposed by the disease and a localized pachymeningitis is present, or a perisinus abscess; or (3) an actual brain abscess is present.

6. Vertigo occurring in the presence of a chronic middle ear suppuration is a serious symptom.

7. Facial paralysis occurring during the course of a chronic suppurative otitis media is an indication for surgical intervention.

Concerning therapy, conservative methods are indicated in Types I and II of chronic middle ear suppuration. This therapy includes one or more of the following procedures:

1. The local use of certain antiseptic solutions or powders.

2. Minor surgical procedures designed principally to remove diseased tissue, proliferative change, and to improve drainage.

3. Removal of any upper respiratory tract pathology which might contribute to inflammation of the middle ear.

The proper choice of a specific major surgical procedure for chronic middle ear suppuration and mastoiditis depends upon the site and type of the pathology. It has been advocated that the term "tympanomastoidectomy" be used in place of the more common designation "radical mastoidectomy." The author has employed three types of operations for chronic otitis media and mastoiditis. These are: (1) The complete simple mastoidectomy; (2) the modified radical mastoidectomy (*tympanomastoidectomy*); (3) the complete radical mastoidectomy (*tympanomastoidectomy*).

Since 1940 the author and his associates at the University of Minnesota have used the Lempert endaural approach for tympanomastoidectomy in a total of eighty-two cases; fourteen of these were of the modified type. During the period these eighty-two patients were operated on by the endaural approach, an additional sixteen were operated on by the postaural route. The advantages of the endaural approach are: (1) There is less soft tissue disturbance. (2) The operative maneuvers are more directly over the middle ear and antrum where usually the most important work is centered. It seems to be a perfect approach for the modified tympanomastoidectomy. (3) The construction of the plastic flap is simplified. (4) Postoperative care and discomfort are lessened.

**Patients Resistant to Sulfonamides**  
—Simon Ball<sup>10</sup> reports on a series of patients suffering from otitis media resistant to sulfonamide drugs. To these

patients penicillin was administered. Of twelve cases of acute otitis media complicating scarlet fever, one required surgical intervention. In ten of the cases, the otitis rapidly responded to treatment. In one case, recovery occurred slowly, which was attributed to the fact that the pathologic condition resembled an acute exacerbation of chronic recurrent suppurative otitis media. Material from the middle ears in these cases yielded, on culture, a growth predominantly *Streptococcus hemolyticus*. *Penicillin* was administered by the intramuscular route in all cases; each dose was 20,000 Oxford units, and the doses were given at four-hour intervals, day and night. The ten cases in which response to treatment was rapid showed resolution of the involvement of the tympanic membrane and restoration of normal hearing in from one to two weeks (average time nine days).

Five cases of acute nonscarlatinal otitis media complicated by mastoiditis were studied. Each patient had been under treatment with a sulfonamide compound and was given penicillin only after signs and symptoms of complicating acute mastoiditis had developed. From the results obtained, it seems that the prompt resolution and healing of acute nonscarlatinal suppurative otitis media complicated by mastoiditis, without the necessity of surgical intervention, is most promising.

**Otitis Externa**—E. Simon<sup>11</sup> states that the frequency and the severity of otitis externa determine its economic importance. His report is based on a group of ninety patients who were observed in a tropical climate and treated until they were well.

The finding of an organism in a culture of material taken from an area of otitis externa does not absolutely indicate that the organism is the primary

invader. It is important to take the material for culture from the infected portion of the canal and throughout the infected area and from the debris when present. The medium used for culture influences the study. A basic factor in the causation of otitis externa is a warm or tropical climate.

In the present study of ninety persons, it was apparent that the otitis was due to bacterial infection. The symptoms of itching, with or without pain, the edema and the discharge usually make the diagnosis certain. With marked edema it may be difficult to determine the presence of otitis media or even mastoiditis. In the latter, the edema of the posterior wall of the canal is rarely as pronounced as that in severe otitis externa, in which often edema of the anterior wall is present. Infrequently there may be otitis media subsequent to otitis externa or *vice versa*; the history will usually indicate the initial infection. With otitis media there are more systemic reactions.

The treatment which was successful in every one of the last sixty cases includes:

1. Thorough *cleansing* and *drying* of the external auditory canal and drum membrane.

2. *Spraying* of the canal wall and drum membrane with a coating of *sulfanilamide*.

3. Administration of *sulfathiazole*, 1 gm. every four hours, and if the aural condition is not improved, 1.5 gm. every four hours. *Sulfadiazine* was used when sulfathiazole was not tolerated.

The routine must be kept up until the discharge and the edema have disappeared and the patient does not notice itching. The average length of treatment for all cases in this series was less than seven days.

**Tinnitus**—M. Atkinson<sup>12</sup> believes that the cause of tinnitus has been studied too exclusively from the purely oto-

logical angle, while the more general neurological outlook has been largely disregarded. Tinnitus could be called, equally well and with greater accuracy, auditory paresthesia. This is merely to translate into pathological terms the physiological concept of the specificity of nerve function that stimulation by whatever means employed, electrical or chemical, of the nerves of any special sense organ produces a sensation appropriate to that organ and to no other.

If this concept of tinnitus and the associated impairment of hearing as evidence of an auditory neuropathy is acceptable, thus bringing the condition into line with peripheral neuritis or neuropathy in general, then the problems posed to the neurologist by this syndrome are the same as those posed to the neurologist by the extremely difficult subject of spontaneous paresthesia.

Experiments suggest that the symptom of tinnitus may have its origin in a vascular disturbance involving the cochlear nerve. Because the same symptom in Ménière's syndrome, which the author has attempted to show also has a vascular basis, has been relieved or improved in a large proportion of cases in the vasospastic group by vasodilatation, it has seemed reasonable to adopt the same method of therapy in similar cases not complicated by vertigo. For, in the opinion of the author, Ménière's syndrome is no other than chronic progressive deafness with tinnitus complicated by a vestibular disturbance. The two are fundamentally the same, etiologically speaking; the difference is only in the spread of the disturbance. *Nicotinic acid* is used as the vasodilator drug of choice. Other drugs have been tried but have been discarded. Nicotinic acid is a powerful vasodilator. It can be given by all routes, intravenous, intramuscular and oral, and should be given by them

all and in that order. The results of treatment of the author's series of cases are given in the table on following page.

The results have been estimated conservatively. Relief means literally what it says, a complete absence of tinnitus, while improvement has had to be definitely asserted by the patient to qualify. Every effort has been made to avoid the pitfall of wishful thinking on the part of the patient, and the series is considered large enough to minimize the inevitable occasional error in this regard. It has been collected over the four years 1940-1943, and a number of these patients have been under continuous observation for more than two years.

It is interesting to note that the greatest percentage of relief or improvement has been obtained in cases of conductive deafness (85 per cent of forty-seven cases), whereas in cases of perceptive deafness only 69 per cent of twenty-two cases have been relieved or improved. This is a finding which would scarcely have been anticipated and which cannot well be explained along the lines of conventional otological thinking. In cases with vertigo the proportion is still less (52 per cent of 106 cases), and this is because in them the disturbance is apt to be more severe (hence its spread) though not essentially different.

**Mastoiditis**—Experience is recorded in treating twenty-three patients having acute surgical mastoiditis by means of primary closure of the mastoid wound and instillation of penicillin into the mastoid cavity. I. F. Johnson, L. Weinstein, and P. S. Spencer, Jr.,<sup>13</sup> believed that since *penicillin* is one of the most effective antibiotic agents known to medical science, this drug administered either locally or generally or both should be the answer to the problem of successful primary suture. It was decided to administer the drug locally primarily because

RESULTS IN TREATMENT OF TINNITUS AURIUM  
WITH NICOTINIC ACID, 1940-1943

<i>Cases</i>	<i>Total Number of Cases</i>	<i>Number with Tinnitus</i>	<i>Results</i>		
			<i>Relieved</i>	<i>Improved</i>	<i>No Change</i>
Deafness of middle ear type only	64	47 (73%)	10 (21%) 40 = 85%	30 (64%)	7 (15%)
Deafness of nerve type only	33	22 (67%)	3 (14%) 15 = 69%	12 (55%)	7 (31%)
Total (Deaf only)	97	69 (71%)	13 (19%) 55 = 80%	42 (61%)	14 (20%)
Deafness and vertigo (Ménière's Syndrome)	106	106 (100%)	13 (12%) 55 = 52%	42 (40%)	51 (48%)
Total, including Ménière's cases	203	175 (86%)	26 (15%) 110 = 63%	84 (48%)	65 (37%)

less penicillin would be required by this method than if the intramuscular route were employed.

Twenty-three patients with suppurative mastoiditis following scarlet fever and measles were treated by simple mastoidectomy and local application of penicillin in the mastoid cavity. Of these, 17 showed complete cure after one course of treatment, while six remained well after a second course of penicillin. The recommended dose of the drug is 10,000 units every eight hours for four days (a total of 120,000 units).

Local application of penicillin in the mastoid cavity through a ureteral catheter after mastoidectomy appears to be a feasible and practical procedure. When this drug is given in proper dosage, healing of the postaural wound and a dry external auditory canal usually are present on the fifth postoperative day. In cases in which aural discharge recurs,

reinsertion of the catheter and reinjection of penicillin for an appropriate period of time produce complete clearing of the discharge. Local treatment with penicillin seems preferable to use of sulfonamide compounds for infections with *Staph. aureus*, hemolytic streptococci, and other organisms susceptible to the antibiotic agent because of the absence of any harmful toxic effects, the slight risk of sensitization, and the increased speed of healing.

**Penicillin Therapy**—*Penicillin* in mastoiditis and its complications is discussed by F. J. Putney.<sup>14</sup> From an experience in the treatment of ten cases, the author concluded that infections of the mastoid and contiguous structures can be readily controlled by penicillin provided the causative organisms are sensitive to the drug. Sterilization of the blood stream and control of spreading infections can be accomplished by

systemic administration of penicillin, but surgical intervention is usually necessary to effect a cure. Local application of the drug has proved beneficial in the healing of persistently draining mastoid wounds.

In eight of the ten cases of the series reported on, *sulfonamide compounds* were administered, without clearing the infection. When penicillin was administered, prompt response was obtained. From the observation and experience made possible by this small group of cases, Putney believes that at the present time penicillin in combination with adequate surgical intervention offers the most effective means of combating the serious and life-endangering otologic complications.

#### **Thrombophlebitis of Lateral Sinus**

—An analysis is presented by H. Rosenwasser<sup>15</sup> of the last 100 cases of thrombophlebitis of the lateral sinus in which operation was resorted to at the Mount Sinai Hospital, New York. The method of treatment generally employed had as its purpose an exposure of the lateral sinus wide enough to encompass the limits of the disease, the opening of the parietal wall of the sinus, the removal of the thrombus when one was present, the excision of part of the diseased parietal wall, and the establishment of free bleeding from the torcular and bulbar ends. If there was doubt as to the safety of leaving the internal jugular vein patent, it was the consensus of the otologic department that the vein should be ligated.

The ages of fifty-five patients ranged up to ten years; the ages of ninety were under thirty years. An obturating thrombus was present in the lateral sinus in twelve of the twenty-seven patients who died; fifteen patients had "suppurative thrombophlebitis" or "mural thrombus" or "phlebitis." In this analysis, it was not possible to correlate pathologic material prognostically with clinical course.

The time at which a metastatic focus becomes clinically evident is no reliable indication as to when the bacteria were deposited. In this study, metastases were noted preoperatively in twenty-one patients, whereas metastases were observed postoperatively in twenty-two patients. Of the latter, nine also had clinical metastases before the operation on the sinus and jugular vein.

There were 27 deaths in this group of 100 unselected patients operated on for thrombophlebitis of the lateral sinus. All operated on were included despite the presence of abscess of the brain and meningitis on admission in a number of them. The mortality from the thrombophlebitis was much higher in old patients (over thirty years) than in children and young adults. Only by including all cases can the inherent mortality of thrombophlebitis of the lateral sinus ultimately be determined.

Nineteen patients were treated by operation combined with chemotherapy; seventeen recovered and two died. The influence of chemotherapy in the treatment of bacteremia is great, and because of this one must beware of the tendency on the part of some to await the effect of chemotherapy alone in cases in which the lateral sinus is involved. Therefore, until substantial evidence to the contrary is advanced, one is justified in assuming that bacteremia due to thrombophlebitis of the lateral sinus will or may persist despite chemotherapy and that surgical measures for the eradication of the phlebotic process are warranted.

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## **RHINOLOGY**

**Sinusitis—Relation of Chronic Sinusitis to Bronchiectasis**—The relationship of chronic sinusitis to bronchiectasis is considered by F. W. Davison.<sup>16</sup>

The author's clinical experience does not permit him to agree with the oft quoted statement that sinus infections cause bronchiectasis. The frequent coincidence of two diseases in the same patient does not prove that one caused the other, but rather suggests that both infections have the same etiologic factors. To evaluate the relationship of these diseases, the author has analyzed the case histories of fifty patients who have bronchiectasis, and the case histories of fifty patients with chronic suppurative sinusitis of at least one year's duration who had no bronchopulmonary symptoms. The diagnosis of bronchiectasis was accepted only when confirmed by bronchograms made with iodized oil. The diagnosis of chronic sinusitis was accepted only if the patient had a history of purulent nasal and post-nasal discharge of at least one year's duration, and if a purulent sinusitis could be demonstrated.

In the series of cases studied, the allergic or hypersensitive state was an etiologic factor in 80 per cent of the fifty patients with bronchiectasis. Edema occurs in all local manifestations of hypersensitiveness. Therefore, it does not seem surprising that bronchial obstruction due to edema, at the time of an acute bronchopulmonary infection, should very frequently lead to the development of bronchiectasis in allergic persons. Seventy-four per cent traced the onset of their chronic cough to an acute bronchopulmonary infection. Mucosal edema is probably the chief factor responsible for the atelectasis which led to the development of bronchiectasis. According to Davison, improved results in the prevention and treatment of bronchiectasis will be had when we know more about hypersensitiveness and how to control it. In the meantime, resort must be had to **bronchoscopic aspiration** to remove viscid, obstructing exudate and the ad-

ministration of **ephedrine** which controls mucosal edema during respiratory infections in hypersensitive persons.

**Therapeutic Trends in Nasal Sinusitis**—O. E. Van Alyea<sup>17</sup> discusses the modern therapeutic trends in nasal sinusitis. He reviews the defense mechanisms of the nose and sinuses and elaborates on the contributing factors to sinus disease.

In selection of nose drops, certain rules should be followed. They should be:

1. Nondetrimental to ciliary action.
2. Slightly acid with a pH of 5.5 to 6.5.
3. Isotonic.
4. Noninjurious to the mucous membrane.
5. Devoid of systemic side effects.

Complying with these requirements are solutions of **ephedrine**,  $\frac{1}{4}$  to 1 per cent in normal saline. Many ephedrine-like solutions in saline are available which also fulfill requirements. Solutions not acceptable as "nose drops" are those containing mineral oil and solutions of mild silver protein.

In cases of nasal blockage even though the septum is deviated, septal resection often fails to relieve the obstruction to breathing. This is because the blockage is in no way related to the septal irregularities. Some of the more common causes of nasal blockage are nasal allergy, systemic disorders which produce vasodilatation in the turbinal structures, and swelling of the nasal tissues which are bathed in the exudate from suppurating sinuses.

The present trend in management is toward conservatism. This is due largely to the fact that there has been marked improvement in our conservative measures. Attention must be directed to the drainage area of the sinus. Simple removal of purulent exudate by lavage is not sufficient unless, in the meantime,

adequate drainage space has been supplied. This may require infraction of the middle turbinate, or antrum window resection. The other sinuses may require special procedures.

The most difficult problem is the "overoperated" case. Although hopeless invalids, in a sense, they are entitled to complete examination and modern therapeutic aids as they are now available in the rhinologic field.

**Aerosinusitis** — A résumé of aerosinusitis is presented by Paul A. Campbell.<sup>18</sup> It is defined as an acute or chronic inflammation of one or more of the nasal accessory sinuses produced by a barometric pressure difference between the air or gas inside the sinus and that of the surrounding atmosphere.

A cavity, such as a normal sinus with an unobstructed ostium, will during ascent allow its gaseous contents to move outward. On descent, the flow of air or gas is in the opposite direction. As this movement is not accompanied by any change in the structure of the sinus, no sensation is felt and no symptoms occur. This free flow of gaseous matter may be altered or prevented by two conditions. First of all, by the presence of pus, fluid, or similar substance covering the ostium; and second, by the obstruction of the ostium afforded by redundant tissue or anatomical deformity. The first situation has been categorized as *nonobstructive aerosinusitis* and the second as *obstructive aerosinusitis*.

Aerosinusitis must be differentiated from purulent and catarrhal sinusitis. There is a history of pain over one or more of the sinuses during or shortly after exposure to extensive barometric pressure change. Epistaxis occurring during or after exposure to barotrauma is extremely suggestive. Roentgenologic plates disclosing opacity or a thickened

lining membrane in the absence of previous sinusitis are strongly indicative. This is especially true if mucosal or submucosal hematomas are demonstrated. Leukocytosis and fever in most instances are absent in aerosinusitis.

The milder cases are self limited, resolution taking place in from a few hours to a few days. The more severe cases may run a course of from a few days to a few weeks. Absorption of mucosal or submucosal hematomas may necessitate a period of from two to six months. When complications ensue, the course may be substantially altered.

From the standpoint of prophylaxis, those who have upper respiratory infections, nasal allergy, or nasal obstruction from anatomical deformity or polypi should not undergo great barometric pressure change until it is known that adequate nasal and sinusal ventilation exists. Shrinkage of the offending structures will usually allow normal ciliary activity to evacuate a sinus of extraneous materials which may have been pressed into it. Obstructive aerosinusitis presents a somewhat different problem. Here the primary objective is to equalize the pressures inside and outside the cavity. A return to the altitude at which the block formed, then emptying the nose of secretion, followed by shrinkage of the offending tissues and slow return to earth would seem the ideal procedure. However, before attempting such a measure, one should know of the underlying pathology before subjecting the patient to further barotrauma. Any procedure which will increase fluid production inside the sinus cavity will influence air pressure equalization. Heat seems indicated. At times it is necessary to move a turbinate or a polyp to break up the block.

Usually, however, shrinkage by any of the usual vasoconstrictor agents will



suffice. Following recovery from aerosinusitis, the nasal passages should be carefully inspected and any obstruction removed before further exposure to altitudinal change.

R. W. Wright and H. M. E. Boyd<sup>19</sup> review the subject of aerosinusitis, its predisposing causes and symptoms, and then proceed to give their observations concerning aerosinusitis at an army air base.

Aerosinusitis is not nearly as common as aero-otitis media. This statement is supported by observation on a year-round basis and covering thousands of flights in the low-pressure chamber. This observation revealed that aerosinusitis occurred in 1.6 per cent of persons while aero-otitis media occurred in almost 6 per cent. The authors believe that the figures for actual flying would be about the same.

Two types of patients were studied: (1) Those experiencing aerosinusitis in the low-pressure chamber as well as some who experienced it in actual flight; (2) patients seen with nasal pathologic changes of moderate to marked extent who had no difficulty in repeated, simulated, or actual flights. Both groups were investigated by visual examination, by study of roentgenograms, by irrigations, and in many cases at operation, at which time the pathologic alterations would be adequately seen.

Changes in barometric pressure are the immediate cause of aerosinusitis. Obstructing pathologic tissue is the underlying or predisposing cause in that it prohibits free passage of air to or from the sinuses. Aerosinusitis cannot develop without both these factors being present.

The symptoms occur chiefly, if not entirely, on descent. The onset may occur almost immediately on descending or more frequently after descending sev-

eral thousand feet. Because of the greater density, as sea level is approached, many symptoms develop during the last few thousand feet. Pain is the outstanding symptom. It is almost always in the area of the frontal sinus, but occasionally it is over the maxillary sinus. The preponderance of pathologic alterations which are thought to be responsible for pain in the region of the frontal sinus are in the antrum. The pain is present only for a short time, usually disappearing in a few minutes to several hours after descent if not before. The pain and the discomfort in the cases of hemorrhage are of longer duration.

The immediate treatment attempts to equalize the differential pressure within and without the sinus. This differential is responsible for the pain. Usually it is a decreased pressure within the sinus with an increasing pressure without, as occurs on descent. An ascent will bring the affected sinus to a level where the trapped air in the sinus will be of the same density as the outside air. There will then exist no differential, and the sinus duct or ostium may open easily, with relief of symptoms. Nasal shrinkage is then used to assure a patent opening. In the low-pressure chamber, leveling off and ascent are standard procedures when it is necessary to secure relief from sinus pains.

The treatment of a well-developed condition will be according to the severity of the symptoms. Usually the pain in the sinus or the headache disappears in a short time and no treatment is necessary other than that for the sinusitis which was present prior to the flight.

For hemorrhages in the sinus mucosa, nothing is done other than waiting for the hemorrhages to absorb. This will take place if the hematoma is not too massive.

*Sinusitis in Children*—The treatment of sinusitis in children is reviewed by B. J. McMahon.<sup>20</sup> He states that the incidence cannot be accurately measured in percentages because of a variance due to many inconstant factors, the most common of which are the environmental influences to which the child is subjected, the manner of living, the housing, the care by the parent or guardian of the well or sick child, injudicious clothing, and improper feeding. It is axiomatic that the more unfavorable the above factors are, the greater will be the incidence of the sinusitis following the common cold, and of the recurrences of the sinusitis until a chronic condition is established. The incidence is greater in the more inclement weather of the winter months, especially in the latter months when the virulence of the infecting organisms has been enhanced by human passage, and the resistance of the child is at a lower level; whereas, in the summer months the rapidly increasing use of swimming pools is also instrumental in causing an increase in the number of sinus infections.

Sinusitis does not occur at any one age more than another. The extent of the involvement is modified in younger children in accordance with the time of development of the sinuses. The ethmoidal and maxillary sinuses are apparently involved in equal proportions, although the latter may be infected from the former because of their more dependent positions.

It has been demonstrated that the two most important mechanisms in the nose are the coating of mucus and the ciliary activity of the mucous membrane, the former functioning as a protective "blanket," and the latter as the motive power to keep this "blanket" moving toward the ostia of the sinuses

and thence to the nasopharynx, carrying its enmeshed bacteria, cell fragments, and foreign particles out of the nasal cavity. The cavernous blood sinuses in the inferior and middle turbinates contrive to keep the tidal air currents properly warmed to protect the lower respiratory passages from an irritation which they are ill equipped to meet.

Inflammation of the mucosa of the nose and paranasal sinuses of a child is more profound than that of an adult, because the constituent structure more easily approaches the embryonal type. The clinical pathological types of sinus infections in children are essentially the same as in adults—namely, the intumescent, the catarrhal, and the purulent. The chronic hyperplastic type of sinusitis is unusual in children, although a polypoid degeneration of the mucosa in allergic states, especially of the antrum, may be encountered.

It is essential to have a clear concept of the predisposing causes, the physiology, and the pathology of sinusitis in children in order to understand and interpret the symptoms and intelligently to plan the treatment. Serious secondary and remote effects of sinusitis may often be the first intimation of this focus of infection and it is but a futile gesture to treat one or the other as separate entities, as it only leads to eventual failure. The treatment should, therefore, be planned according to a simultaneous local and constitutional regime.

The constitutional imbalance should be properly adjusted by an adequate diet, removal of offending allergens, and supplementary vitamin therapy. The environmental predisposing factors should be corrected as well, as it is within the jurisdiction of the otolaryngologist to do so. Therapeutic aids should be used as

indicated—*calcium, iron, and thyroid* medication.

Every effort should be made to treat the local infection as intensely as conditions permit by the use of suction, non-irritating intranasal medication and displacement irrigations. Nasal irrigations carefully administered with *physiologic sodium chloride* solution are beneficial in liquefying and removing the purulent secretions, and preparing the nose for carefully instilled intranasal medication.

Certain serious constitutional diseases have their origin in latent as well as manifest sinusitis which may at times be unsuspected. The ultimate success of the treatment of sinusitis in children depends upon the cooperation between the otolaryngologist and the pediatrician.

**Diseases of Paranasal Sinuses**—An interesting symposium on disease of the paranasal sinuses was presented by staff members of the Mayo Clinic.<sup>21</sup>

In discussing the symptoms and methods employed in diagnosis, W. C. Thornell stresses the fact that in chronic hyperplastic sinusitis in which nasal polyps are associated with infection, headache may be present and may be referred to any region about the head. The nasal polyps may or may not be due to allergic disease. Headaches are uncommon in chronic suppurative sinusitis but are common in the combined type of sinusitis. Complaints of frontal or facial pain alone are not diagnostic of sinusitis in the absence of physical sign. Nasal or postnasal drainage of a purulent or mucopurulent character is the predominant symptom in most chronic infections of the sinuses. All patients who have postnasal drainage are not suffering from sinusitis. The cause may be some pathologic conditions in the pharynx.

O. E. Hallberg discussed the roentgenologic aspects of the paranasal si-

nuses. He answers the pertinent question: "When should a rhinologist or a referring physician send his patient for roentgenologic examination of the sinuses," thus:

1. He should be sent when definite manifestations of sinus disease, such as external fistulas, either through the skin or somewhere along the alveolar process, are present.

2. He should be referred if he gives a history of recurrent bouts of acute sinusitis which might be suspected of chronic sinus involvement.

3. Roentgenograms should be made of the sinus region of patients who insist they have chronic sinus disease.

4. Pathologic changes in the nose, such as pus, changes in the mucous membrane, nasal allergies, polyps, and so forth, found in the course of routine examination of the ears, nose, and throat are an indication that patients should undergo roentgenologic examination.

5. Patients who have certain pulmonary conditions, such as chronic bronchitis, bronchiectasis, or bronchial asthma, in which sinuses often are involved, should have roentgenologic examination.

6. Patients who have headaches of an indeterminate type should have roentgenograms of the sinus region made.

7. When the presence of a benign or malignant neoplasm is suspected in the paranasal sinuses, roentgenologic examination is indicated.

The treatment of sinusitis was reviewed by H. L. Williams. He divides sinusitis into five separate categories: (1) Fulminating sinusitis; (2) acute sinusitis; (3) subacute sinusitis and recurring acute sinusitis; (4) chronic sinusitis; and (5) hyperplastic sinusitis. The latter type of sinusitis is defined as a mixture of allergic and infectious sinusitis. In divisions 2 and 3, treat-

ment is primarily medical; in the fourth, it is primarily surgical.

The early treatment of fulminating sinusitis is a *trephine opening* into the *frontal sinus* followed by *lavage* of the *sinus* with some oxygen-liberating agent as *peroxide of hydrogen* to establish aerobic conditions in the frontal sinus and thus *get rid of the anaerobic organisms* which produce the especially dangerous type of osteomyelitis. Trefphine openings should be made through a portion of the frontal sinus which does not contain diploic tissue—in other words, the floor of the sinus. Nichols and the author recently demonstrated that the organisms present in the spreading type of osteomyelitis are destroyed by *penicillin*. If dead bone is present, however, this must be removed surgically, in addition to penicillin therapy, or the osteomyelitis will recur after apparent cure.

In acute sinusitis the relief of pain and the institution of drainage are the considerations of prime importance. *Roentgen therapy* is the best single treatment for the relief of the intense pain in the stage of engorgement of acute sinusitis. *Sulfonamide therapy* is also useful in the acute stage of sinusitis before a large collection of pus has more or less inhibited the action of the sulfonamides. Of great importance is the avoidance of traumatizing manipulations such as antrum punctures in the acute stage of the disease.

In subacute and recurring acute sinusitis, the *Dowling pack* followed by gentle interrupted *suction* is a most effective remedy. If shrinkage of the nasal membranes is followed by gentle suction with the patient's head placed in such a position that drainage through the natural ostia is favored, resolution of the infection usually will take place. In protracted subacute sinusitis, it is

sometimes useful to perform lavage of the involved sinus through the natural ostium, or if the ostium has become occluded, through puncture in the inferior meatus.

In chronic sinusitis, treatment is usually surgical as compared to acute and subacute sinusitis for which treatment is usually medical except, as the author mentioned, in the case of fulminating sinusitis. Occasionally adjunct surgical procedures must be carried out to restore physiologic conditions of the sinus. If adjunct procedures are not needed in disease of a single sinus, a simple surgical procedure to secure adequate drainage and aeration of the sinus is the only procedure necessary. Care should be taken to preserve in so far as possible the mucosal lining of the sinus.

Treatment of pansinusitis is considered in two categories: Namely, treatment in cases of pansinusitis associated with bronchiectasis and treatment in ordinary cases of pansinusitis. Cases of pansinusitis associated with bronchiectasis present certain special problems. The sinusitis does not produce the bronchiectasis but usually the bronchiectasis and sinusitis have been produced by some severe respiratory infection which has left both conditions present. It is important that suppuration in the sinuses be cleaned up, because if the disease in the sinuses is eliminated, much is accomplished toward eliminating the infection in the bronchiectatic cavities and consequently many of the symptoms. It has been found that with the use of *penicillin* to prevent postoperative osteomyelitis, the extensive surgical procedure necessary to clean up the pansinusitis present can be done with safety.

The author discussed also so-called infectious sinusitis with which allergic disease usually is present. The headache

in this condition probably is due to the allergy. Since chronic sinusitis responds readily to properly directed surgical management, the difficulties in securing relief in this condition must also depend on the presence of the allergy. For these reasons the recognition of the allergic background in these cases is of paramount importance. Relief will not be secured until the necessary surgical procedures are combined with adequate and intelligent treatment directed toward relieving the fundamental functional disorder of the nasal and sinal tissues.

**Penicillin Therapy in Sinusitis**—Cognizant of results being obtained in the treatment of streptococcic and staphylococcic infections with penicillin, I. J. Hauser and W. P. Work<sup>22</sup> believed that this drug should also be effective in the therapy of certain types of sinusitis. They employed *penicillin* in a small series of cases at first. When the results proved highly satisfactory, they treated all patients showing early chronic suppurative sinusitis with adequate amounts of penicillin intramuscularly, without regard to causes, before considering any type of surgical intervention. Not only is penicillin an important adjunct to other forms of treatment for sinus disease but, even more important, it has proved highly effective in the management of its complications. The method of choice of the authors consisted of the intramuscular injection of 20,000 units every three hours until the optimum result was obtained.

In the treatment of orbital cellulitis *penicillin* has proved so dramatically effective that it has replaced every other method of treatment. In cases of allergic rhinitis with superimposed infection, while it eliminated all evidence of supuration, it did not effect a permanent cure inasmuch as the underlying pathologic state, allergy, was still present.

Patients with chronic suppurative sinusitis of relatively short duration can apparently be cured by *penicillin* alone. In long-standing chronic suppurative sinus disease, however, penicillin alone appeared to have little if any value; used in conjunction with adequate surgical treatment of such diseases it accomplished rapid and complete cures.

**Carcinoma of the Antrum**—The site and direction of extension of carcinoma of the antrum have definite prognostic significance, according to M. F. Snitman.<sup>23</sup> The prognosis has been influenced also by an increasing knowledge of radiation therapy especially as it pertains to its technical application. The plan of treatment consists of the application of *radium* within the cavity as a supplementary measure to external protracted irradiation, after exposure of the antrum by conservative surgical intervention. The results of this technic have been highly satisfactory and have obviated the necessity of radical operation.

In the consideration of a therapeutic regime, it is essential to consider two chief factors—the site of the primary lesion and the presence or absence of lymphatic extension. Lesions in the floor of the sinus with involvement of the hard palate and alveolar ridge are amenable to intraoral surgical removal, followed by local radium application. Treatment of the primary lesion is not affected by the presence of regional metastases. If metastases are present, a new therapeutic problem presents itself.

Patients with cancer of the head and neck present one of three conditions in the cervical region: (1) No palpable metastatic nodes; (2) operable nodes; (3) inoperable nodes. The management of the nodes of these groups at the Tumor Clinic of the University of Illinois follows closely the plan as outlined at the Memorial Hospital, New York

City. No prophylactic dissection or irradiation is performed. If the nodes are operable and the control of the primary lesion is assured, *neck dissection* is performed. If the nodes are inoperable, the patient is submitted to *external radiation* supplemented with *radon seed implantation*.

In the opinion of the author, protracted fractionated irradiation appears to be an extremely favorable adjunct in the treatment of antrum carcinoma. While our therapeutic weapons have not changed in recent years, our end results have improved because we are learning to apply them with greater effectiveness.

**Myalgia**—The syndrome of physical or intrinsic allergy of the head, so-called myalgia of the head (sinus headache) is reviewed and elaborated on by H. L. Williams.<sup>24</sup> He holds that one of the principal tasks of the rhinologist is analysis, whenever possible, of various types of headache. His observations based on a study of 118 cases of myalgia of the head indicate a tendency for involvement of certain muscles or muscle groups in myalgia of the head and neck. Since myalgia of the head can be readily confused with other painful conditions about the head, certain diagnostic criteria for myalgia have been established. These diagnostic criteria should serve to distinguish myalgia of the head from psychogenic headache, migraine, glossopharyngeal neuralgia, and primary and secondary fibrositis.

Headaches of muscular origin were first treated by *heat* and *massage*. Because of the concept that myalgia was a physical allergy associated with histamine, treatment was attempted with *histamine* as outlined by Horton. Great individual variation in the response to this drug was encountered, so *nicotinic acid*, which had proved successful in the treatment of labyrinthine hydrops, was

tried. An initial dose of 25 mg. of *niacin* was given; this dose was increased by a like amount daily until a dose which relieved symptoms was reached. This usually proved to be 100 mg. daily by hypodermic injection. It was found that the same dose given by mouth, night and morning, usually would maintain this relief. Some individual variation in the tolerance to niacin was found but this was unusual. After two or three months of daily treatment with niacin, it was found that relief would be continued when 100 mg. of niacin was administered by mouth three times a week. Fifty-four of seventy-two patients who had myalgia and were treated with niacin obtained relief. The concept that what patients call "sinus headache" frequently is a physical allergy involving muscle called myalgia of the head and neck, must be borne in mind.

**Meatal Approach to Maxillary Sinus**—It is the contention of O. E. Van Alyea<sup>25</sup> that the meatal approach to the maxillary sinus for the purpose of irrigation is rapidly gaining favor. This seems especially true as more and more rhinologists become acquainted with the advantages of this route over that of the inferior meatus. Anatomic studies have demonstrated that, in approximately 50 per cent, the maxillary or an accessory ostium is readily available for catheterization, in 30 per cent it may be reached but with difficulty, while in the remaining 15 per cent the ostium is entirely inaccessible. In a majority, then, irrigation of the antrum may be carried out by the way of the normal ostium without difficulty and with little annoyance to the patient, and this alone should justify a widespread adoption of the procedure.

The method which now removes the need of bony puncture in antra irrigation is described as follows: The middle

meatus alone is anesthetized. The membranous area is probed carefully for an accessory opening. The cannula tip is brought forward into the hiatus semilunaris between the bulla and the uncinate process. As the space between these two structures narrows down, the tip is rotated downward and should pass into the normal ostium. This contact is prevented if the hiatus is too narrow at the point adjacent to the opening, or if a large turbinate prevents rotation. In any event, little time is spent in probing; the dull-tipped cannula is exchanged for one with a sharp point and the membranous wall is penetrated without further ado.

**Irrigation** of a sinus, regardless of the method of approach, is an effective therapeutic measure in certain types and stages of sinus disease. It is not used during the early stages of an acute attack. In chronic infections, sinus irrigation is generally regarded as of little value. When confronted with a persistent maxillary sinus infection, the rhinologist often includes with his diagnostic measures a roentgen study with iodized oil in the sinus. Proper management of a persistent sinus infection, along with the correction of drainage defects, may require several irrigations. The manner in which these irrigations are carried out often has considerable bearing on the extent of cooperation to be expected from the patient.

**Osteomyelitis of the Frontal Bone**—In the opinion of J. Otte,<sup>26</sup> general and local infection and trauma play a causal rôle in osteomyelitis of the frontal bone. Fever, pain, and edema are the prominent symptoms. Edema may prove to be chief diagnostic sign of chronic osteomyelitis and is a definite indication for roentgenologic investigation of the condition of the frontal bone. In treatment, extirpation of the diseased

bone and drainage is imperative. Extreme situations may be prevented by early and radical treatment of frontal sinusitis which generally precedes disease of the frontal bone.

**Chronic Sinus Disease Therapy**—Successful therapeutic measures in chronic sinus disease are those which spring from a sound knowledge of the anatomy, the physiology, and the histopathology of the structures treated. O. E. Van Alyea<sup>27</sup> calls attention to the fact that the earlier rhinologists had no such chart to guide them as is shown by their apparent disregard for the preservation of functional structures. The methods adopted without a proper scientific foundation were largely unsuccessful and it is only within recent years that the reason for previous failures has been ascertained.

All measures advocated now for treatment of nasal and sinus disease must undergo careful scrutiny in the light of our better understanding of the function of nasal and sinus tissues. At present considerable attention is directed toward an improvement of methods for combating chronic involvements. The mucosa which lines the sinus cavities is regarded as a defensive membrane capable of carrying on indefinitely and of restoring itself to a normal state under favorable conditions. The essentials for repair are provided by the institution of adequate sinus drainage and this is accomplished by the removal of drainage barriers from the neighborhood of the sinus ostium. These barriers may be anatomic or pathologic and are often corrected by simple measures.

In the event of failure to unblock the sinus outlets, a new opening is often indicated and this should be accomplished without disturbing the functioning tissue. Seldom is the radical removal of the sinus mucosa indicated. If it is instituted, it should be with the under-

standing that the procedure offers no assurance of complete and permanent termination of the existing disease.

## LARYNGOLOGY

**Cancer of the Larynx**—It is the discovery of the laryngoscope in 1885 that laid the foundations for the accurate study of laryngeal cancer, according to Rao.<sup>28</sup> It is still true that cancer of the larynx is uncommon as compared to the occurrence of carcinoma in other parts of the body. Half a century has passed since Krishaber proposed the classification of laryngeal carcinomata into extrinsic, intrinsic, and mixed types.

There were only seventy-five patients suffering from malignant growths of the larynx and the laryngopharynx admitted to the Ear, Nose and Throat Department of the King George Hospital, during the last fifteen years. Cancer of the larynx was discovered in twelve cases and cancer of the laryngopharynx in sixty-three cases. The essential cause of the disease remains as obscure as that of carcinoma in general. Excluding post-cricoid area, extrinsic as intrinsic disease is five times more common in the male than in the female. It is now established that endolaryngeal cancer is met with most commonly on the vocal cord. The subglottic area is the next favorite location and it is rare in the ventricular band or in the sinus of Morgagni and almost unknown in the interarytenoid region.

The mortality of the untreated cancer of the larynx and laryngopharynx is 100 per cent. Treatment is curative and palliative. The accepted methods of curative treatment are *surgery, irradiation*, and a combination of both.

*Laryngofissure* is the method of choice where the growth is small and

limited to the middle of the vocal cord whatever be the estimate of its malignancy by the histological examination. *Laryngectomy* is indicated in patients in whom the growth involves the entire length of the cord and the arytenoid region or the aryepiglottic fold. Certain other operations are described, most of them being merely modifications of laryngofissure or complete extirpation of the organ.

*Radiation* has a large field of application as a palliative measure of treatment. Irradiation also has its use in combination with surgery.

Little has been achieved in permanent success in the author's series of cases. While at the present time the results are disappointing, the future is hopeful with earlier diagnosis and provision of adequate facilities of treatment.

*Histopathological Study of the Larynx*—The significance of histopathologic study of serial sections in carcinoma of the larynx is emphasized by M. F. Snitman.<sup>29</sup> Microscopic study of a block of laryngeal tissue removed by thyrotomy revealed incomplete removal of the cancer *in situ* of the right true cord. The need for further biopsy was clearly indicated, a later study disclosing residual malignant tissue in the larynx. In the absence of a serial study of the involved cords, the residual malignant tissue would have been permitted to invade further, with development of clinical signs of recurrence. The extent of the growth may have been such as to indicate laryngectomy. However, delay has been avoided, and further laryngofissure should give a favorable prognosis.

A true picture of the laryngeal pathologic changes could not be determined from the original biopsy specimen, which showed a hornifying squamous cell lesion without carcinoma *in situ*. This observation is in accord with the estab-



lished fact that it is often difficult to make an accurate microscopic diagnosis from one portion of a tumor. An examination of serial sections of the entire mass is essential.

It is therefore sound to conclude, according to the author, that serial histologic study of laryngofissure specimens would prevent delay in the management of residual malignant neoplastic tissue.

Carcinoma of the larynx gives an earlier indication of its presence than carcinoma elsewhere in the body, in the opinion of P. H. Holinger and R. G. Rigby.<sup>30</sup> In spite of this, the mortality from carcinoma of the larynx is still high; partly because the patient refuses to seek medical attention for what to him is merely an annoying symptom without pain and partly because in the early, curable stage of the carcinoma, the patient receives temporary symptomatic relief from topical remedies. Not infrequently these are applied without an examination of the larynx, whereas no diagnosis of carcinoma of the larynx can be made without histologic proof of the presence of the malignant growth.

The treatment still resolves itself into surgery or irradiation. The choice of therapy is determined by the histological character of the tumor, its location and extent within the larynx, the degree of motility of the vocal cord, the presence or absence of cervical glands, and the general condition and age of the patient.

When the carcinoma is localized to the middle third of the cord, and the cord is movable, a *laryngofissure* is indicated. This procedure will result in the cure of 85 per cent of such patients dependent upon the degree of differentiation of the tumor. Small lesions in the anterior commissure may be similarly treated, using the anterior commissure technic described by Jackson.

When the carcinoma has extended along the cord to produce fixation of the cord or has extended somewhat subglottically and is grade I or grade II in histologic character, the therapeutic procedure of choice is a *laryngectomy*. More highly malignant tumors with similar involvement respond more satisfactorily to *irradiation*. The presence of glands in the neck changes the prognosis at once; they may be resected or treated by interstitial irradiation dependent upon their extent.

When the carcinoma is extrinsic, or when it is intrinsic but highly malignant in character, irradiation is indicated. Irradiation is indicated in otherwise operable cases if the age, temperament, or general condition of the patient contraindicates surgery.

Early recognition and treatment make carcinoma of the larynx a curable disease.

**Esophageal Speech**—In the opinion of W. F. Zinn,<sup>31</sup> the significance of hoarseness has not been given the recognition it deserves in view of the frequency with which this symptom is encountered in various diseases and the seriousness of the conditions which follow in its wake. Hoarseness is defined as "alteration in the speaking voice which results in a roughened or rasping character to the voice." This alteration may be produced by impairment of the function of any one of the several parts that go to make up the speech mechanism.

Hoarseness may result from the following conditions:

1. Inflammatory infections of the larynx—the more common being acute and chronic laryngitis, tuberculosis, lues, diphtheria, influenza, measles, and scarlet fever.

2. Trauma—including all types of wounds to the larynx, internal and external.

3. Tumors—benign and malignant.

4. Disturbances of the central and peripheral nervous systems—including aneurysms, brain tumors, and any condition producing pressure or injury to the recurrent laryngeal or vagus nerves, and hysterical aphonia.

Of all the cases of hoarseness examined by the author, tumors, or neoplasms, either benign or malignant, have been found in the largest number of cases. It is now pretty well conceded that 80 per cent of all cases of carcinoma of the larynx are curable by operation if the diagnosis is made while the disease is still intrinsic. The three diseases most responsible for hoarseness—cancer, tuberculosis, and lues—can all be present at the same time in the larynx, and the discovery of one does not rule out either of the other two. Laryngeal tuberculosis is usually secondary to the pulmonary condition and is a late development of the disease. In syphilis, as in tuberculosis, the lesion is rarely primary and diagnosis is made by supportive tests.

As total extirpation of the larynx is performed more and more often for malignant tumors, it becomes necessary, according to E. T. Gatewood,<sup>32</sup> that the laryngologist interest himself more and more in the problem of esophageal speech. The laryngologist, of course, gives more thought to the diagnosis and extirpation of cancer than he does to restoring the function that the organ performed. In recent years, however, a few American laryngologists have made a concerted effort to restore to these patients a voice which may be their own.

The artificial larynx is serving a good purpose in many instances. However, when it is considered in conjunction with esophageal speech, the disadvantages are numerous. While curing the patient is, of course, first consideration in dealing with cancer, voice develop-

ment is of definite concern to the patient if he attempts to regain his former economic and social station in life.

There are several factors which influence the development of esophageal voice: (1) The will of the patient to learn, which is especially essential; and (2) the encouragement and confidence that may be imparted to the patient by one who has had a like operation and has acquired a satisfactory voice.

The physical requirements for a substitute voice are an air chamber and a glottis capable of vibrating. A small semiflexible catheter not larger than a No. 6 is inserted through the nose into the esophagus with its distal end resting in the upper third of the esophagus. The catheter is then anchored to the tip of the nose for placement. By attaching a bulb to the proximal end, air is furnished the esophagus by gentle pressure. The esophageal glottic folds are assumed to be very flaccid in contrast to vocal cords, and the insertion of a fine catheter does not seem to interfere with their approximation or vibrations. This procedure seems particularly helpful to the beginner until he can at least partially acquire an air chamber or is able to exercise better glottic control. While the tube has a very distinct practical value, it also has a definite psychologic effect. The patient is immediately encouraged when he experiences the sensation that he is definitely aided in making a sound when air is supplied the tissues that are capable of vibrating. The inflow of air is equivalent to esophageal inspiration and its action may be likened to a synthetic lung. Expiratory pressure serves to help accelerate the column of air during the practice of phonation contractions. By repeated vocal efforts, vibratory quality and tension of the soft tissue folds are gradually acquired.

Eructation may be encouraged at the outset and it serves a good purpose in getting the patient started. The most perfect pseudovoice is usually exhibited by those who develop the nerve cell habit of very frequently inspiring small quantities of air into the esophagus between their words or sentences with no obvious effort. They often attain a fine degree of modulation and frequently a range of one to one and a half octaves. Patients who can acquire such a voice may return to their former station in life with a certain degree of satisfaction.

**Acute Laryngotracheobronchitis—**Acute laryngotracheobronchitis is not a specific disease entity, in the opinion of H. L. Baum.<sup>33</sup> It is rather a clinical syndrome produced by a combination of factors, certain of which are man made. It is probably primarily influenzal in origin, with secondary invaders, most often the streptococci entering the picture later to contribute their share of the damage. The only highly effective specific treatment now available is that with human convalescent serum, primarily *anti-influenzal* and secondarily *anti-streptococcic serum*. With such serums the disease may be shortened and the development of the later complications sometimes avoided.

Management of the subglottic edema becomes of first importance when swelling threatens the integrity of the airway. Intravenous use of concentrated human plasma may solve this problem satisfactorily, enabling one to avoid tracheotomy. The osmotic action of the hypertonic plasma protein withdraws the fluid of edema from the interstitial tissue spaces of the subglottic space and the tracheobronchial mucosa into the blood stream.

Successful management of laryngeal obstruction without tracheotomy also avoids those serious sequelae, progressive tra-

cheobronchial dryness, and subsequent formation of plugs, with obstruction, and is therefore greatly to be desired. Intubation is the operation of choice, especially early, and a combination of both intubation and tracheotomy may frequently be of advantage to minimize tracheobronchial dryness.

Breathing of moist, cool oxygen at all times and high humidity of the respired air, especially following tracheotomy, are fundamental in the management of this disease.

**Late Tonsillar Hemorrhage—**H. Neivert and his co-workers<sup>34</sup> have been conducting investigations of the causation and the prevention of late tonsillar hemorrhage. They now bring to light that these hemorrhages occur frequently as a result of the postoperative administration of acetylsalicylic acid for its analgesic effects. The complete absence of late secondary tonsillar hemorrhage in a series of patients operated on and kept on an acetylsalicylic acid-free postoperative regimen added credence to the surmise that the bleeding is induced by acetylsalicylic acid. Some surgeons, without being aware of the implications, gave no acetylsalicylic acid postoperatively, and they did not observe bleedings. Others used vitamin K empirically and claimed to have no hemorrhages.

These facts were substantiated when Link and co-workers (1943) showed that salicylic acid and sodium salicylate administered repeatedly or even in single doses, orally or intravenously, induced hypoprothrombinemia in rats kept on a ration low in vitamin K. The animals could be protected against this action of salicylic acid by administration of a vitamin K preparation.

These facts throw light also on our particular problem of late posttonsillectomy bleeding and its causation. Hypo-

prothrombinemia interferes with coagulation. From investigations by Neivert and his group, it was revealed that in some subjects a total daily dose of 2.4 gm. of acetylsalicylic acid will produce an elevation in prothrombin time on the very next day, whereas in others it will be much longer before a significant rise will be discernible—but, most assuredly, such a rise will occur eventually.

If acetylsalicylic acid is an etiologic factor in the occurrence of late posttonsillectomy hemorrhage, it would seem logical to eliminate it from the postoperative routine. In view of the fact, however, that acetylsalicylic acid, by virtue of its effectiveness and its comparative nontoxicity, is the most widely used analgesic, it was thought advisable, rather than to eliminate it, to combine it with an agent which will counteract its effect on prothrombin. Proof was established that the water-soluble vitamin K-like compound, *synkavite* (tetrasodium 2-methyl-1, 4-naphthohydroquinone diphosphoric acid ester), prevents this undesirable side-effect of acetylsalicylic acid. There is no justification for looking on acetylsalicylic acid in general as a dangerous drug. It is not a common cause of hemorrhage in man, as proved by the many millions of doses of the drug taken with impunity every year. But when a wound is healing by second intention, such as that following tonsillectomy, a hypoprothrombinemic state should be avoided. The authors do not believe that the prothrombinopenia induced by acetylsalicylic acid must in all cases lead to secondary posttonsillectomy bleeding.

According to R. Singer,<sup>35</sup> the nature of the postoperative course is not influenced by the surgical method of removal, the type of anesthesia employed, or the age or the sex of the patient. The incidence of secondary bleeding is prac-

tically negligible in the operating clinics and hospitals of Central Europe; textbooks published in Central Europe do not mention it. Inasmuch as the methods of operation and the technics employed in this country and in Europe are the same, it appears obvious that the difference in the postoperative course is due to some other factor. It was first assumed that the occurrence of secondary tonsillar hemorrhage was predicated on climatic or nutritional factors. However, on a comparison of preoperative and postoperative regimens used in this country and abroad, only one significant difference could be found. This was the administration in this country of acetylsalicylic acid to relieve postoperative pain. Considering this drug as being the etiologic factor of the hemorrhagic inflammation and secondary hemorrhage observed in so many patients, the author completely eliminated the use of acetylsalicylic acid and salicylates postoperatively. In seventy-five patients observed during 1943 with an acetylsalicylic acid-free posttonsillectomy routine, there was no secondary hemorrhage and, still more significant, not a single hemorrhagic inflammation of the soft palate. The postoperative course of the entire group followed the pattern of the normal healing process.

From these experiences and those of other investigators, it seems reasonable to assume that the prothrombin-lowering effect of salicylates is a plausible explanation for the occurrence of secondary posttonsillectomy hemorrhage. Serious consideration has to be given to this factor because of the widespread use of salicylates as analgesics.

### Thornwaldt's Disease

The communication of A. R. Hollender and P. B. Szanto<sup>36</sup> describes the pathologic anatomy of so-called Thorn-

waldt's disease and emphasizes that the syndrome, characterized primarily by occipital headache and postnasal discharge, is the same whether produced by inflammatory changes in the bursa or in the median recess. Therefore, in the opinion of the authors, the term Thornwaldt's disease is a misnomer, because it does not convey this impression from a clinical point of view. The

called nasopharyngeal bursa in autopsy material and concluded that the rhinoscopic clinical observations of Thornwaldt have a sound morphologic basis, but it is irrelevant whether the inflammatory changes are in a true nasopharyngeal bursa or in a median nasopharyngeal recess.

Bursa pharyngea is rare. It is a diverticula-like structure in the midline of

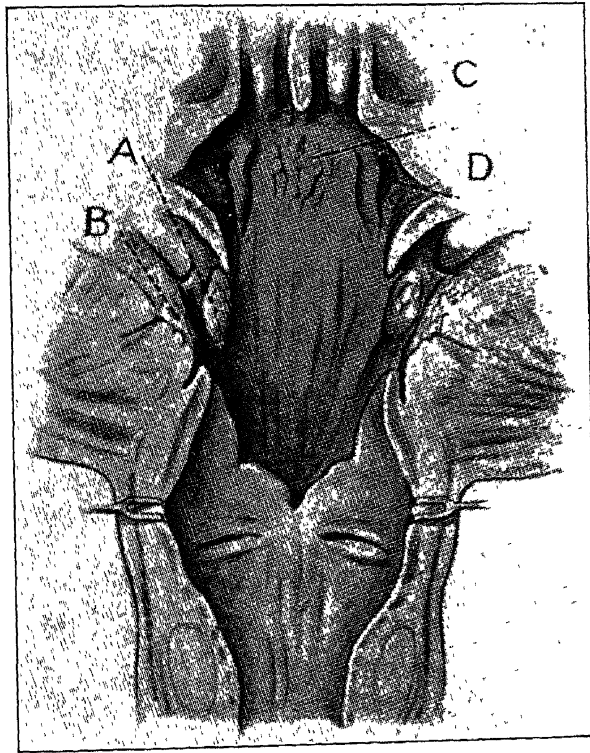


Fig. 1—Waldeyer's ring (semischematic): *A*, Palatine tonsil; *B*, lingual tonsil; *C*, nasopharyngeal tonsil; *D*, tubal tonsil. (Hollender, A. R. and Szanto, P. B.: *Arch. Otolaryng.* 41:291 (April) 1945.)

more appropriate designation would seem to be Thornwaldt's syndrome. The present study is based on 140 consecutive autopsies in which the nasopharynx was carefully examined, especially from a pathologic point of view.

Of the publications dealing with this problem, the more important is one by Poelschen (1890). He studied the pathologic changes (described by Thornwaldt in his monograph, 1885) of the so-

the posterior wall of the pharynx at the lower end of the pharyngeal tonsil, directed upward and backward. The apex of the bursa is attached to the periosteum of the occipital bone just before the pharyngeal tubercle of the body of this bone. It should be stressed that neither the nasopharyngeal bursa nor the posterior recess is in itself pathologic. It requires microscopic examination to differentiate between a median recess and

a pharyngeal bursa. An infected pharyngeal bursa and an infected median recess may lead to the clinical rhinoscopic and gross pathologic picture of Thornwaldt's disease, as it is now understood. Because of this fact, the authors suggest, as more appropriate and accurate, the designation Thornwaldt's syndrome for what has

developmental and involutional changes of the lymphatic apparatus occur in the same sequence.

The development of the nasopharyngeal and tubal tonsils begins after birth and attains its peak between the second and third years of life. At puberty the involution of these structures generally



Fig. 2—Specimen from a woman 75 years of age: *A*, Nasopharyngeal tonsil showing marked hyperplasia; *B*, septum nasi; *C*, posterior wall of the pharynx; *D*, epiglottis. (Hollender, A. R. and Szanto, P. B.: *Arch. Otolaryng.* 41: 291 (April) 1945.)

up to the present time been called Thornwaldt's disease.

**Lymphatic Tissue of the Nasopharynx**—The most commonly accepted concept concerning the development and involution of the lymphatic tissue of the nasopharynx, according to A. R. Hollender and P. B. Szanto,<sup>37</sup> is the so-called craniocaudal development of Waldeyer's ring. This concept holds that the

approaches completion. The development of the palatine tonsils may begin early in infancy but usually later than that of the nasopharyngeal and tubal tonsils. The involution of the palatine tonsils is observed in the majority of persons after the fourth decade of life. The lingual tonsils comprise the final link in Waldeyer's ring and exhibit maximum development in adults at about this same

DISTRIBUTION OF THE STAGES OF DEVELOPMENT AND INVOLUTION OF LYMPHATIC TISSUE  
(WALDEYER'S RING) IN ONE HUNDRED AND THIRTY-ONE AUTOPSY  
SPECIMENS ACCORDING TO AGE GROUPS

	20-35	35-50	50-65	65-75	Over 75
Nasopharyngeal tonsil					
Completely involuted.....	5	10	35	30	14
Partially involuted.....	2	4	7	8	4
Moderately well developed.....	..	..	2	1	..
Well developed, hyperplastic.....	3	1	1	1	3
Tubal tonsil					
Involuted.....	8	12	42	39	16
Partially involuted.....	..	1	2	..	3
Moderately developed.....	1	..	1	1	1
Well developed, hyperplastic.....	1	2	..	..	1
Palatal tonsil					
Involuted or very small.....	1	1	4	4	3
Small or moderately developed.....	6	12	37	34	13
Hyperplastic.....	3	2	4	2	5
Lingual tonsil					
Moderately developed.....	8	14	37	36	17
Well developed, hyperplastic.....	2	1	8	4	4

period. In elderly persons the lingual tonsils are usually well preserved.

The observations recorded in this report were made on autopsy material—131 adult specimens were available for gross or microscopic study, or both. The table shown above details the incidence of partial and of complete hyperplasia of the lymphoid structure of Waldeyer's ring according to different age groups. Figure 2 is that of a specimen from a woman seventy-five years of age showing marked hyperplasia of the nasopharyngeal tonsil but involution of the palatine tonsils, and moderate development of the lingual tonsils.

Partial involution of the nasopharyngeal tonsil was a common observation. After complete involution, a deep median recess may remain (Fig. 3). This should not be confused with a nasopharyngeal bursa.

Hyperplasia of the nasopharyngeal tonsil in adults is not always associated

with clinical symptoms. Two factors commonly influence the production of symptoms: (1) Infection; (2) size of the nasopharyngeal vault. The latter is the more important factor.

In their conclusions, the authors stress the fact that hyperplasia of the nasopharyngeal tonsil is not a rare occurrence in adults; the incidence of hyperplasia of the tubal tonsil is less frequent. They emphasize, furthermore, that the nasopharyngeal tonsil may be the only structure in Waldeyer's ring presenting hyperplastic changes.

There is no correlation between the stage of development of the nasopharyngeal tonsil and other pathologic processes in the body. It is reasonable to assume that certain constitutional factors are responsible for variations in the development and involution of the different parts of Waldeyer's ring.

**Chemotherapeutic Agents — Penicillin Therapy in Peritonsillar and**

**Pharyngomaxillary Spaces**—A. J. Cone<sup>38</sup> reports on his results with local infiltration of *penicillin* solutions in peritonsillar and pharyngomaxillary spaces. Penicillin as a prophylactic local infiltration just prior to a tonsillectomy was used in two patients during a three-month period. During the same period, twenty-eight routine local tonsillectomies

ical standpoint, healing was facilitated.

No patient receiving peritonsillar or parapharyngeal injections of penicillin, alone or combined with novocaine, showed any untoward reaction. The abscess cases were improved, two cases clearly without surgical drainage. Surgical drainage was facilitated in two patients with parapharyngeal abscess.



Fig. 3—Specimen from a man 69 years of age. *A*, Septum nasi; *B*, deep median recess; *C*, adhesion in Rosenmüller's recess on the right. (Hollender, A. R. and Szanto, P. B.: Arch. Otolaryng. 41: 291 (April) 1945.)

were done. All patients were observed for reactions. Solutions were made in physiological sodium chloride solution and contained 5000 units per cc. From 1 to 2 cc. were used in deep peritonsillar injections just prior to tonsillectomy after the routine infiltration with novocaine. No instance of reaction, *i. e.*, edema or hives, occurred. From a clin-

From this study the author concludes that (1) penicillin in physiologic sodium chloride solution in dosages of 5000 to 10,000 units is well tolerated when used as a peritonsillar infiltration; (2) penicillin combined with novocaine has proved valuable when surgical drainage of peritonsillar or parapharyngeal abscess has become necessary; (3) as-



piration in cases of parapharyngeal infection permits earlier localization and drainage of collection of pus.

**Penicillin Therapy in Hemolytic Streptococcus Pharyngitis and Tonsillitis**—Penicillin therapy in hemolytic streptococcal pharyngitis and tonsillitis is discussed by N. Plummer *et al.*<sup>39</sup> A group of patients with severe acute pharyngitis-tonsillitis were studied clinically and bacteriologically. In twenty-eight of forty-five positive cases that had cultures positive for group A (Lancefield) hemolytic streptococci, **penicillin** was given intramuscularly in a dosage of 15,000 units every four hours over periods varying from twenty-four hours to six days; **sulfadiazine** was given in eleven cases and no specific therapy in six.

Penicillin was found to exert a pronounced effect on the number of hemolytic streptococci in the nasopharynx. Discontinuance of the drug produced a gradual return of hemolytic streptococci to the nasopharynx. In nineteen patients treated by the authors with penicillin for sixty-four hours or more, symptomatic relief commenced in eight to twelve hours after the beginning of therapy and was complete in twenty-four to thirty-six hours. However, clinical relapse of the pharyngitis-tonsillitis occurred in four of the nine patients treated for less than four days but in none of the ten treated for six days. Relapses and complications always were associated with the presence or reappearance of hemolytic streptococci in the nasopharynx.

This study reveals further evidence of the high antihemolytic streptococcal action of penicillin and emphasizes its value in dangerous hemolytic streptococcal infections. It is believed that penicillin in minor hemolytic streptococcal infections may be beneficial, but further investigation will be required

to ascertain its exact indications and contraindications in these conditions. It is of practical value to appreciate the greater effectiveness of penicillin in hemolytic streptococcal pharyngitis and tonsillitis and to urge its use without delay in any serious, progressive hemolytic streptococcal infection.

**Infectious Mononucleosis**—Infectious mononucleosis, although a benign disorder, may simulate and consequently be confused with more serious diseases of the lymphatic glands, according to J. H. Press, E. L. Shevin, and A. P. Rosen.<sup>40</sup> The disease is characterized by irregular fever, sore throat, enlargement of the lymph glands, spleen, and liver, and lymphocytosis. Although no responsible agent has been identified, staphylococci, streptococci, Vincent's organism, *Bacterium monocytogenes hominis*, and toxoplasma have been implicated, and a possible relationship to leukemia, syphilis, rubeola, and influenza has been suggested.

The many clinical varieties may be classified as: (1) Glandular type, in which lymph node enlargement is predominant, observed especially in children; (2) anginose type, characterized by occurrence of sore throat, after one to three weeks of pyrexia and malaise, often with diphtheritic-like membranes of or around the tonsils; and (3) febrile type, which is noted most frequently among adults, and distinguished by sudden onset of fever, headache, and malaise, and a macular or papular rash.

The incubation period is one to twenty-eight days and the illness may be mild and clinically unrecognizable or severe, persisting for weeks or months. Although leukopenia may exist in the early stages of the disease, leukocyte counts of 10,000 to 20,000 are usually present by the second week and counts up to 63,000 have been reported. The characteristic cell is

an atypical but mature lymphocyte which, with normal erythrocyte and platelet counts, differentiates the blood picture from that of acute leukemia. Agglutination of sheep erythrocytes by the sera of these patients in titers of 1:128, a positive Paul-Bunnell reaction, occurred in sixty-four of ninety tested cases. A positive serologic reaction for syphilis, present in 40 per cent of the cases for a few days, is due to the transient occurrence of another antibody than that responsible for the Paul-Bunnell reaction.

**Sulfathiazole Therapy in Vincent's Angina**—Treatment of Vincent's angina with sulfathiazole is considered by W. W. Manson and I. T. Craig.<sup>41</sup> Inasmuch as *arsenicals*, as well as *bismuth*, are far from the specifics that they were once believed to be in the treatment of infections of this type, the authors adopted the treatment recommended by Linton — *sulfathiazole* dissolved on the tongue. By doing so, the treatment time in the average case of Vincent's angina has been cut from ten days to seventy-two hours.

The treatment consists of a 0.5 gm. sulfathiazole tablet dissolved on the tongue every two hours during the day and two such tablets dissolved in the same manner every four hours at night. The temperature usually returned to normal in twenty-four hours and the symptoms had almost completely disappeared by that time. In spite of the clinical improvement, the treatment was continued for a total of seventy-two hours, except in very mild cases, when it was terminated at the end of forty-eight hours. Lesions were invariably cleared up in ninety-six hours after beginning treatment. There were no cases of sulfonamide sensitivity in this series. The results have been so satisfactory in the cases treated by the authors that they have adopted this method as the

routine treatment of all cases which demonstrated clinical Vincent's angina.

The effectiveness of *penicillin* in the treatment of Vincent's angina is discussed by B. M. Schwartz.<sup>42</sup> It was found to be of definite value in the treatment of fourteen cases. The recommended dose is 100,000 units administered in 20,000-unit doses every three hours. In mild cases smaller doses may be required and in unusually severe cases larger doses may be directed.

P. L. Shallenberger, E. R. Denny, and H. D. Pyle<sup>43</sup> also present their experiences with penicillin treatment of Vincent's angina. Their experience with a group of cases seems to justify the conclusion that topical application of penicillin in a concentration of 500 units per cubic centimeter applied four times daily is a completely and rapidly effective therapeutic procedure in the treatment of Vincent's infection.

**Upper Respiratory Tract Infections**—It is the contention of R. L. Cecil<sup>44</sup> that sufficient time has not yet elapsed for a thorough investigation of the possibilities of chemotherapy in upper respiratory tract infections.

Although it is generally recognized that virus infections are unaffected by *sulfonamides*, many practitioners have administered one of the sulfonamides to patients with the common cold with the idea of preventing complications. There is no particular point in giving either sulfonamides or penicillin for hemolytic streptococcus sore throats unless infection is severe. In the severe cases, either *sulfadiazine* or *penicillin* should shorten and mitigate the attack. It seems quite possible that for sinusitis, penicillin will displace the sulfonamides. For ear infections, the sulfonamides have been quite helpful. Mastoidectomy is reduced 50 per cent by prompt sulfonamide therapy.

Severity and duration of acute bronchitis can be mitigated by the use of sulfonamide therapy, but a great deal depends on the responsible bacterial agent.

**Inhalation Therapy**—E. W. Hagens, M. Karp, and C. J. Farmer<sup>45</sup> present a preliminary report on the inhalation method for penicillin therapy. Their study was suggested by the article of Bryson, Sansame, and Laskin, appearing in *Science*, July 14, 1944, in which the aerosolization of solutions of penicillin was described. Hagens *et al.* give the details concerning the apparatus and method employed in their studies. Twenty-two patients were treated with penicillin by the inhalation method. Urine and blood levels show that the drug is absorbed from the lungs to a sufficient degree to offer another method when penicillin therapy is indicated. The authors believe that the inhalation method probably has an additional advantage over the other methods of administering penicillin, due to its local effect. For this reason the inhalation of penicillin may be the method of choice in cases of pulmonary disease.

The inhalation of penicillin results in temporary improvement in bronchiectasis, but the condition frequently lapses back shortly after therapy is discontinued. In most cases gram negative bacteria are encountered so that another antibiotic substance is also necessary, one to which bacteria are sensitive.

Asthmatic patients who have a superimposed bronchial infection with an organism to which they possibly are allergic may be favorably influenced by treatment.

Acute pulmonary conditions respond to the inhalation treatment, and the method may be used advantageously in children and in other patients when the usual methods of treatment, such as the

intravenous or the intramuscular injection of penicillin, are unsuitable.

**Penicillin as an Antibiotic**—According to M. H. Mothersill,<sup>46</sup> an antibiotic is defined at the present time as a metabolic product of one micro-organism which is capable of inhibiting or destroying some other micro-organism. In order that an antibiotic may also be a systemic anti-infective, it must be able to circulate safely in the body and inhibit a pathogen. *Penicillin* is at present the outstanding antibiotic.

As for the sulfonamides, the earlier one, such as sulfanilamide, caused cyanosis, acidosis, hemolytic anemia, and various signs of toxicity to the nervous system such as dizziness, incoordination, and even psychosis. Sulfathiazole, sulfadiazine, and sulfamerazine do not cause cyanosis or acidosis, and are less likely to cause hemolytic anemia or central nervous system symptoms. While they are more effective than sulfanilamide for equal concentrations, due to their lower solubility these drugs may obstruct the urinary tract with crystals. Their solubility in urine is decreased by acidity and increased by alkalinity.

The possibility of the patient becoming allergic to the sulfonamides has been a source of concern. The percentage of patients capable of developing hypersensitivity is low but unpredictable. Another handicap is the fact that the activity of the sulfonamides is reduced by the presence of pus.

All these shortcomings and handicaps of the sulfonamides led to a desire for a new anti-infective which would be more potent and devoid of disadvantages. The answer was penicillin. As a local and systemic anti-infective, this drug is usually more active against pyogenic cocci than the sulfonamides. It is, however, ineffective against gram negative bacilli. Infections due to some of

these are susceptible to sulfonamide therapy. Penicillin appears to have value in the treatment of certain infections, such as syphilis, diphtheria, and tetanus, in which the sulfonamides are useless.

In otorhinolaryngology, penicillin is used at times as a local and at times as a systemic anti-infective. It has been used with good results in appropriate cases of acute otitis media. It has been used also in osteomyelitis of the frontal bone, but attempts to depend solely upon penicillin without the aid of surgery have been disappointing. Its benefit in sinusitis depends upon whether the cause or complication is due to a penicillin-susceptible organism. The local application of penicillin will give better results in acute than in chronic maxillary sinusitis. In chronic infections, penicillin will perhaps be more effective if used to supplement surgical operations.

The question of whether penicillin will be given locally or systemically, or both, depends upon circumstances.

F. J. Putney<sup>47</sup> emphasizes that penicillin must not be used indiscriminately, but its effectiveness in combating susceptible infections is benefiting practically every branch of medicine. The acute conditions have afforded the most gratifying results, while in chronic diseases the response has been hard to evaluate. In osteomyelitis, penicillin has not supplanted surgical procedures but helps materially in combating the disease. Adequate drainage by surgical intervention in addition to penicillin is necessary to effect a cure in the majority of cases. Penicillin has proved equally effective against sulfonamide-resistant organisms. All of Putney's patients were given only penicillin, and none was treated by a combination of this drug and sulfonamides. Patients who had failed to respond to the sulfonamides improved under penicillin to the same degree as

those that had not received sulfonamide therapy. In osteomyelitic infections, granulations have been made healthy, and draining purulent wounds have become sterile while the patients were receiving penicillin.

In chronic osteomyelitis of the frontal bone, it is possible to obtain healing under penicillin therapy without resorting to extensive surgery, and a thorough trial of penicillin lasting over several months may be necessary. When there is no regression under this form of treatment the involved sinus should be operated on and this procedure in addition to penicillin therapy may prevent further extensive operations. Brain abscess, extradural abscess, and orbital cellulitis occurred as complications in three cases of osteomyelitis without apparent bearing on the response to the drug. The longest period of treatment was that of a patient with osteomyelitis of the superior maxilla and frontal bones. Prompt and complete healing was obtained in orbital cellulitis with vanishing of pain within the first twelve hours of treatment.

Putney's experience with other nose and throat diseases was limited to a few cases of suppurative sinusitis treated both locally and systemically and several cases of peritonsillar and lateral pharyngeal abscesses in which the drug was given intramuscularly. The infections of the pharynx usually recovered without incision, although this method is not recommended as healing would have followed more rapidly if drainage has been instituted. In a case of chronic purulent infection of the maxillary sinuses, cultures became sterile, but the discharge continued and, at operation, the membrane was thickened with chronic inflammatory changes present. Acute infections of the maxillary sinuses have been cured after several irrigations with penicillin,

even when the organism was a staphylococcus that had proved resistant to other forms of treatment. The strength of the solution employed locally was 250 units per cubic centimeter. Preliminary investigation of Vincent's infection of the mouth and tonsils indicates rapid healing, with disappearance of organisms after a few days of systemic penicillin therapy.

The author believes that at the present time penicillin, in combination with adequate surgical treatment, offers the most effective means of combating some of the serious and life-endangering complications encountered in otolaryngology.

H. L. Williams<sup>48</sup> reviews the problem of chemotherapy in otolaryngology. He proposes three principles for general guidance.

1. Since chemotherapeutic agents now available are only active against the gram positive cocci and bacilli, the causative organism should be determined before potentially dangerous drugs are administered, except in such conditions where the gravity of the infection outweighs the danger of the drug.

2. In mild infections, such as the common cold where the incidence of complications has been estimated at about 1 in 1000, a drug capable of producing more frequent and serious complications in itself should not be employed.

3. If the drug is used at all, the dose should be adequate to produce the desired effect. The usual dosage is, roughly, 0.065 gm. (1 grain) of the drug to every pound of body weight per twenty-four hours, with an initial dose of one third to one half of the estimated twenty-four hour total. In mastoiditis and otitic meningitis, a blood concentration of the usual sulfonamide drugs used should be maintained at 15 to 20 mg. per 100 cc. of blood. Because of the rapid excretion of the drug, it should be given at regular

intervals around the clock and the practice of giving the drug during the daytime only should be deprecated.

In any case in which the sulfonamide compounds of penicillin are to be used, collections of pus should be drained and necrotic tissue and bone removed.

*Sulfadiazine* is recommended as the sulfonamide of choice for almost all infections. With this drug, 0.13 gm. (20 grains) of *sodium bicarbonate* should be administered every four hours to prevent kidney complications. With *penicillin* there is no evidence that any toxic action is produced.

The best method of administration is the continuous intravenous drip. Forty thousand Oxford units are dissolved in 1 liter of isotonic salt solution, or in a 5 per cent solution of dextrose in a triple distilled water. Initially 200 cc. of this solution are administered at a fairly rapid rate. Thereafter the rate of administration is regulated to about 35 drops per minute. Penicillin may be administered intramuscularly into the gluteal region, using 10,000 to 20,000 units dissolved in 2 to 4 cc. of isotonic salt solution every three hours. In William's experience, twice as much penicillin is required intramuscularly as intravenously to produce a comparable clinical result.

The author has not found the use of a 5 per cent solution of *sulfathiazole* in the nose, as advocated by Turnbull, of any benefit in the treatment of chronic and subacute sinusitis. He has given treatment of sinusitis with solutions of gramicidin, tyrothricin and penicillin by means of the Proetz displacement technique considerable trial and is very much disappointed in the results.

In cases of acute sinusitis, acute otitis media and acute mastoiditis, the oral administration of chemotherapeutic agents may be of value in the stage of engorgement before the purulent foci

are created. After this has taken place, the pus must be drained and the necrotic tissue removed, after which the sulfonamide may be continued as an adjunct.

In cases of spreading osteomyelitis of the frontal bone, *penicillin* is of decided advantage. The treatment of acute fulminating frontal sinusitis should begin with a trephine opening into the floor of the frontal sinuses to avoid opening into cancellous tissue, followed by irrigations with some solutions like hydrogen peroxide to establish aerobic conditions within the sinus together with the use of penicillin. All pockets of pus must be drained and all the necrotic bone must be removed. With penicillin therapy, this may be done through a coronal incision which may be closed with superficial drainage only. This form of treatment avoids the open dressing of wounds and everted skin flaps which conditions later require multiple plastic operations for closure.

In otitic meningitis the intrathecal administration of penicillin is recommended because of the failure of penicillin to penetrate the hematoencephalic barrier. The dose should be 10,000 Oxford units dissolved in 2 cc. of *sodium chloride* solution, combined with adequate doses of *sulfadiazine*. After the patient has made an apparent recovery, small doses of sulfadiazine should be continued for ten days to prevent a recurrence of the infection.

**Sulfonamide Therapy**—Since the introduction of the sulfonamides, considerable controversy has arisen concerning their value as a local remedy. A. R. Hollender<sup>49</sup> believes, however, that they have proved beneficial and effective for a large number of surgical and nonsurgical indications. They have been utilized in various forms, the solution and the powder being most suitable for topical application.

In more than 100 cases of nasopharyngitis, the author used *sulfathiazole* powder in the treatment. Shrinkage of the membranes should precede insufflation of the powder by a compressed air powder blower or a hand blower. In the acute cases, treatments are given daily in the office, and for home use each patient is supplied with a small amount of powder which he uses one extra time during the day as a snuff. As compared with other topical remedies for pharyngitis, the powder treatment gives every indication of being effective in relieving the symptoms more promptly and in shortening the course of the disease. In the chronic cases a number of applications may be necessary, but they should be given at intervals of several days. While toxic reactions thus far have not been observed, sensitivity should be guarded against.

**Sulfathiazole Chewing Gum**—Studies to determine the effect of sulfathiazole in chewing gum in certain oropharyngeal infections were conducted by Noah Fox *et al.*<sup>50</sup> The choice of chewing gum as the vehicle seemed indicated, because it offered possibilities that the drug would not be rapidly extracted from the gum and swallowed. The question as to the most efficient sulfonamide drug was resolved by studies of the salivary levels of sulfonamide compound attained by apparently normal adult subjects, while chewing gum tablets containing sulfanilamide, sulfathiazole, or sulfadiazine for one hour. The solubility of sulfathiazole (1:1060 at 98.6° F.), intermediate between that of sulfanilamide and sulfadiazine, not only allows a constant and sustained extraction of the drug from the chewing gum but also provides a definitely bacteriostatic concentration of sulfathiazole in saliva throughout a full hour of chewing. From these experimental data it seems that chewing gum con-

taining sulfathiazole rather than sulfanilamide or sulfadiazine is preferable for local chemotherapy of oral and pharyngeal infections susceptible to sulfonamide drugs.

The best clinical results are obtained in those conditions of the mouth and pharynx in which the beta hemolytic streptococcus is the preponderant etiologic organism. It should be noted that apart from the effect described, the chewing of nonmedicated gum is in itself a mouth-cleansing process.

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## CLINICAL PATHOLOGY

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### Hepatic Disease

#### Serum Lipids in Hepatic Disease<sup>1</sup>

—Recent observations suggest that hypolipemia occurs as a result of extensive degeneration or destruction of the parenchyma of the liver. The most frequent disorder is an increase usually relatively and absolutely of free cholesterol and a decrease or deficiency of cholesterol esters. In biliary obstruction, total serum cholesterol and lipid phosphorus rise. After the obstruction is relieved, the serum level of these substances returns to normal. In biliary cirrhosis and infectious hepatitis, cholesterol and lipid phosphorus are found at normal or subnormal levels in a certain number of cases. In portal cirrhosis, the serum levels of these lipids tend to fall as the disease progresses. Toxic hepatitis and some cases of infectious hepatitis are characterized by reduced levels of these lipid components.

**Mechanism of Positive Cephalin Cholesterol Flocculation Reaction in Hepatitis<sup>2</sup>**—A hypothesis for this mechanism suggests that the gamma globulin component of normal serum fails to bring about flocculation because of an inhibitory action exerted by substances in the albumin fraction. In disease, a positive flocculation may be obtained with serum altered as follows:

1. Increase of gamma globulin in such quantity that there is insufficiency of the normal components of the serum albumin fraction to inhibit the reaction.

2. Diminution of the serum albumin fraction.

3. Diminution of the flocculation inhibiting properties of the albumin fraction.

The positive test observed in hepatitis is probably a combination of all of these factors. Emphasis might be placed upon the third condition, namely, modification of the albumin fraction, because electrophoretically separated albumin fraction of normal serum tends, when in sufficient amounts, to inhibit flocculation of gamma globulin, while the albumin fraction of serum from cases of hepatitis shows relatively less inhibition.

Flocculation is apparently affected by exposure to light. Either sunlight or the light of an electric bulb increases the sensitivity of the reaction.<sup>3</sup>

**Evaluation of the Maclagan Thymol Turbidity Test**—The thymol turbidity test is based on the concept that globulins are more or less readily precipitated by phenolic compounds. The technique of the test has been previously published.<sup>4-5</sup> Watson<sup>6</sup> has compared this test with the cephalin cholesterol flocculation test on 252 samples of serum from 145 individuals. Thirty-one of these subjects were considered as normal and 60 were suffering from infectious hepatitis. Watson found the Maclagan test more often negative than the flocculation test in cases of severe liver disease. Once the disease is established, it appears that the Maclagan test is fully as useful as the Hanger flocculation test. It is evident that the underlying mechanism of the two tests is not identical and therefore one cannot employ the former as a substitute for the latter. The Maclagan test can be employed for serial observation in a case where the diagnosis has been established. There is no information concerning the reaction in early stages of hepatic disease. Be-



cause of its simplicity and because the test may be completed in thirty minutes instead of forty-eight hours, it may be employed to advantage in the differential diagnosis of jaundice if its limitations are kept in mind.

**Serum Proteins in Portal Cirrhosis**—Stacey<sup>7</sup> investigated the serum proteins in thirty-six cases of portal cirrhosis in the natives of Iraq. The diet of these people was deficient in protein; and, although a high protein intake for a period of two weeks failed to cause a rise in serum protein, further investigation is required to ascertain whether failure to absorb digested protein plays any part in causing the changes observed. Stacey employed the Greenberg method for the determination of total protein and albumin and a method derived from the Proske and Watson technic (1939) for the determination of euglobulin. He observed:

1. Serum euglobulin was above normal in all patients with cirrhosis, the average being four times the normal value.

2. Serum pseudoglobulin was within the normal range, but the average was raised. This rise was significant.

**Bilirubinuria**—The increased incidence of infectious jaundice and the demand for a procedure which will reveal small amounts of bilirubin in the urine prompted Hawkinson<sup>8</sup> and her co-workers to investigate and improve the Harrison test. Especially was this desirable after the observation of Neefe and Stokes that bilirubin may appear in the urine in experimentally induced hepatitis before there is elevation of total serum bilirubin.

**Reagents Required**—Pieces of extra thick filter paper (Schleicher and Schull number 470) are allowed to remain briefly in a saturated aqueous solution of barium chloride. They are dried in

air or in an oven, then cut into strips four inches long and one-half inch wide. Cotton swabs may be utilized if suitable thick paper is not available.

**Fouchet's Reagent**—Trichloroacetic acid (25 per cent aqueous), 100 cc.; ferric chloride, 0.9 gm.

**Procedure**—One end of a barium chloride impregnated strip of paper is placed in the urine sample and held about one half immersed in the vertical position for a period of one to two minutes. The paper strip is then placed on a towel or other absorbent material to remove the excess urine. Inspection will reveal slightly more color in that portion of the strip which was held at the level of the surface of the urine. Drop one or two drops of Fouchet's solution on this area. If bile is present in the urine, a green color will develop which varies in intensity with the amount of bilirubin present. Smaller amounts of bilirubin will produce a faint green line running across the strip. The cotton swabs are similarly employed. The result with the swab is not so sharp as with the paper strip.

**The Methylene Blue Test**—Gellis and Stokes<sup>9</sup> employed a modified methylene blue test in the study of infectious jaundice. They found it of value in the diagnosis of preicteric hepatitis, in evaluating the course of the disease, and the prediction of impending relapse. The simplicity of the test enhances its value as a diagnostic procedure.

**Procedure**—To 5 cc. of prebreakfast urine, add two drops of 0.2 per cent aqueous solution of methylene blue chloride. If a green color develops, add methylene blue dropwise until a blue color develops. If more than five drops are required, the urine must be diluted and correction made for the dilution. Dilution is necessary because the intensity of the color produced makes it

difficult to determine the endpoint. Tests performed on 1000 patients with diseases other than hepatitis revealed that in 74 per cent only two drops of dye were required to produce a blue color; 24.3 per cent required three drops; and 1.7 per cent required four drops to change the initial green color to blue. A test of five drops or more is considered positive. The test was positive in thirty-three cases of infectious hepatitis one to six days before scleral icterus was apparent. At the time of the test the icterus index was normal in twelve cases and the remaining twenty-one were in the upper limits of normal or only slightly elevated. In convalescence, the methylene blue test became negative, although clinical jaundice was present and the icterus remained elevated. The mechanism of this test has not been determined.

#### **Hormone Tests for Pregnancy**

The hyperemia test using infantile rats is, according to Zondek *et al.*,<sup>10</sup> adequately accurate for the determination of pregnancy but is not sufficient for the examination of disturbed pregnancies such as ruptured ectopic pregnancy, threatened, incomplete, or missed abortion. In these cases, the chorionic gonadotropin is decreasing and prolan B is no longer detectable. It is these hormones which produce the hyperemic effect. Therefore, a negative result might well be obtained when these conditions exist. The follicle-stimulating hormone (prolan A) is still present and will be revealed by any one of the tests which depend upon the occurrence of a blood dot (hemorrhagic follicle).

#### **Acute Infectious Lymphocytosis**

This condition, probably first recognized by Smith and reported in 1941, was previously confused with infectious

mononucleosis and still must be carefully differentiated from leukemia. It is a disease of children. Birge and Hill<sup>11</sup> have reviewed the literature concerning this disease and point out the occurrence of an increase of the lymphocytes in the blood and spinal fluid. Total absolute lymphocyte counts in the blood have been as high as 116,000 (97 per cent of total white cells). The lymphocytes seen in the stained film are morphologically normal and mostly of the small variety. There is no anemia; the heterophile antibody reaction is negative. Lymphocytes are found in the aspirations of bone marrow.

#### **Seminal Smears in Sterility**

The morphology of the spermatozoa is of as much value in the study of fertility in the male as the relative number. Keaty and Hamblen<sup>12</sup> have evolved a rapid method for demulsification of seminal fluid and staining of the smears which eliminates artefacts and reveals morphologic detail. They recommend the preparation of thin and thick smears of the ejaculate after spontaneous liquefaction has been established. The delay in making the smear should not extend beyond two hours. The smear is placed immediately in a 1 to 1 mixture of absolute alcohol and ether for thirty seconds. It is washed in, first 50 per cent alcohol, then in distilled water for one to two seconds. Demulsification is accomplished by placing the smear in a solution consisting of eight drops of concentrated hydrochloric acid in 40 cc. of distilled water. The slide remains in this solution until it is no longer opaque. It usually requires one to two minutes for opacity to disappear. The slide is then washed in distilled water for one to two seconds. Stain is accomplished as follows:

1. Stain in a 1 per cent aqueous solution of eosin yellow thirty seconds.
2. Wash in 50 per cent alcohol one to two seconds.
3. Stain in Harris hematoxylin one minute.
4. Wash in tap water one to two seconds.
5. Stain in fast green (F.C.F. 0.5 per cent aqueous solution) one second.
6. Wash in 95 per cent alcohol one to two seconds.
7. Wash rapidly in absolute alcohol one to two seconds until the film appears clear of stain.
8. Clear in xylol three minutes.
9. Cover with Clarite.
10. Cover with a cover-glass.

By this technic the mature components reveal a pink nucleus, a blue acrosome, a green body and tail. Developmental forms, spermatocytes and spermatids, reveal a purple nucleus and a blue-green cytoplasm. Other components, such as cytoplasmic fragments attached to immature cells, are stained green. The nuclei of leukocytes are purple to dark blue. Epithelial cells, green.

### Diagnosis of Uterine Cancer by the Vaginal Smear Method

**Diagnosis of Uterine Cancer by the Vaginal Smear Method**—Papanicolaou (1941) was the first to call attention in 1928 to the presence of carcinoma cells in the vaginal secretions of women suffering from carcinoma of the uterus. His original technic has been modified a number of times for the sake of simplicity. There is no question that this method of diagnosis is of great advantage in the early recognition of carcinoma of the uterus, and it permits of an accurate diagnosis in many cases without resorting to the more conventional biopsy, to which the patient may not be willing to subject herself and which requires an even more elaborate procedure. It is likewise obvious that both the collection of the material and

the interpretation of the findings in the smear require technical skill and a knowledge of this special form of cytology. Smith<sup>13</sup> and his co-workers have proposed a simple modification which in their hands has worked satisfactorily. The author has used it with complete satisfaction, with a full realization of its shortcomings, namely, that a negative result is of no significance. Operation is not to be advised on the smear alone and the conventional biopsy should be performed on all cases reported as positive. In their experience with 813 cases studied, positive cases were called negative in 7.1 per cent; negative cases were labeled as positive in 2 per cent. The technic followed by these workers is as follows: Insert a long, dry pipet with attached rubber suction bulb, compressed, to the fornix of the vagina. Release the bulb and withdraw the pipet. Blow the material on a glass slide, fix while wet with a solution consisting of equal parts 95 per cent alcohol and ether. Stain by Papanicolaou's method.

Carcinoma cells are recognized by the criteria generally adopted, namely:

1. Disproportionate size of nucleus to cell mass. *In normal cells the nucleus represents from one fifth to one third the entire mass of the cell; while in cancer cells most of the cell is occupied by the large nucleus.\**

2. Variation in the size of nuclei in cell groups. *The normal cells are characterized by a rather definite uniformity of cell and nucleus size; while in malignant disease both vary in the same field.*

3. *Coarseness of chromatin markings. The chromatin markings of normal cells are relatively delicate and numerous compared with those of malignant cells. In the latter the chromatin appears denser and in fewer and in larger markings.*

4. *Occasionally mitotic figures may be observed. If these do not conform to the usual pattern of mitotic figures, this lack of conformity is in favor of a diagnosis of malignancy.*

\* Author's comment in italics.

### The Rh Blood Types

According to the studies of Weiner,<sup>14</sup> there are at least three sorts of anti-Rh agglutinins (Fig. 1). The most common variety corresponds exactly with the standard antirhesus immune animal serum of Landsteiner and Weiner agglutinating the cells of 85 per cent of people. It is designated anti-Rh<sub>0</sub>. The second variety agglutinates approximately 70 per cent of white individuals and is designated anti-Rh'. The third, the rarest, is designated anti-Rh''; it causes only 30 per cent positive reactions. The matter is complicated by the observation that the agglutinins, anti-Rh' and anti-Rh'', usually occur in association with anti-Rh<sub>0</sub>, thus producing two additional varieties of human anti-Rh serums, namely, anti-Rh<sub>0</sub> plus anti-Rh', designated as anti-Rh<sub>0</sub>Rh', and anti-Rh<sub>0</sub> plus anti-Rh'', designated anti-Rh<sub>0</sub>Rh''. The cells reacting with these agglutinins or combinations of agglutinins are similarly named.

Blood reacting with agglutinin anti-Rh' only and not anti-Rh<sub>0</sub> or anti-Rh'' is designated Rh'.

Blood reacting with agglutinin anti-Rh<sub>0</sub> only is designated Rh<sub>0</sub>.

Blood reacting with agglutinin anti-Rh'' only is designated Rh''.

The combinations of blood reacting with anti-Rh<sub>0</sub> and anti-Rh' are designated Rh'<sub>0</sub> or, more simply, Rh<sub>1</sub>, and blood reacting with anti-Rh<sub>0</sub> and anti-Rh'' is designated as type Rh'<sub>0</sub> or, simply, Rh<sub>2</sub>.

Considering the two agglutinins, anti-Rh' and anti-Rh'', there are four classes of people which these agglutinins determine just as the agglutinins  $\alpha$  and  $\beta$  determine four groups. The agglutino-gen which reacts with anti-Rh' is labeled by Weiner U; that agglutino-gen reacting with anti-Rh'' is labeled V; and W designates the recessive gene anal-

TABLE I  
THE EIGHT RH TYPES AND THEIR GENOTYPES

<i>Rh type</i>	<i>Genotypes</i>
Negative	rrrh
Rh'	Rh'Rh' and Rh'rh
Rh''	Rh''Rh'' and Rh''rh
Rh'Rh''	Rh'Rh''
Rh <sub>0</sub>	Rh <sub>0</sub> Rh <sub>0</sub> and Rh <sub>0</sub> rh
Rh <sub>2</sub> (Rh' <sub>0</sub> )	Rh <sub>1</sub> Rh <sub>1</sub> Rh <sub>1</sub> rh Rh <sub>1</sub> Rh'
	Rh <sub>1</sub> Rh <sub>0</sub> and Rh'Rh <sub>0</sub>
Rh <sub>2</sub> (Rh' <sub>0</sub> )	Rh <sub>2</sub> Rh <sub>2</sub> Rh <sub>2</sub> rh Rh <sub>2</sub> Rh''
	Rh <sub>2</sub> Rh <sub>0</sub> and Rh''Rh <sub>0</sub>
Rh <sub>1</sub> Rh <sub>2</sub> (Rh' <sub>0</sub> Rh' <sub>0</sub> )	Rh <sub>1</sub> Rh <sub>2</sub> Rh <sub>1</sub> Rh'' Rh'Rh <sub>2</sub>

ogous to O of the A, B, O series reacting to neither. Bloods reacting to both are designated UV.

When the agglutinin, anti-Rh<sub>0</sub>, is brought into the picture six allelic genes must be postulated instead of three because each of the genes, W, U, V, comprises two Rh genes as follows:

W — Rh + Rh<sub>0</sub>

U — Rh<sub>1</sub> + Rh'

V — Rh<sub>2</sub> + Rh''

Weiner's table of phenotypes and genotypes (top of page) clarifies this picture.

**The Hr Factor**—Most (90 per cent) of the instances of intragroup reactions or erythroblastosis occur as the result of Rh sensitization. A few of the remainder are due to isoimmunization to other factors, M, P, A, and O. The most common cause of intragroup incompatibility in Rh positive people seems to be the Hr factor. It was discovered by Levine and others that rarely a serum of an Rh positive person will agglutinate all Rh negative bloods and those Rh positives which did not react with anti-Rh' serum. The symbol Hr indicates a factor opposite to Rh because it is present in Rh negative bloods.

**Technic of Rh Tests**—Blocking antibodies must be considered. These antibodies have the ability to combine with Rh positive cells without causing agglu-

tination so that if subsequently a good anti-Rh serum is added, no agglutination occurs. Before human anti-Rh sera can be employed for Rh typing, their specificity must be determined. The technic of specificity determination and the titration of sera is complicated and beyond the scope of the average laboratory. It is fully discussed in Weiner's review. It is safest to obtain the typing serum from some one of the supply houses which market a diagnostic serum after *complete*

sediment appears granular (Fig. 1). The tubes may now be *gently* shaken or flicked once or twice with the finger. Clumps will be observed by the naked eye in positive reactions. Further examination with a low power lens will reveal the smaller clumps. It must be cautioned that more than gentle shaking will break up the clumps and a positive reaction will appear negative. If the reaction is doubtful, allow the tubes to stand for an additional two hours or

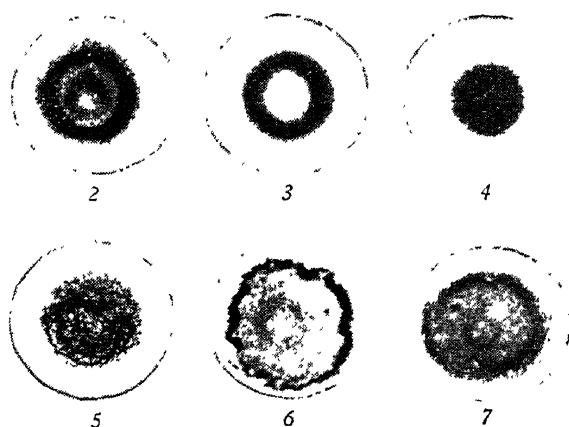


Fig. 1—Sedimentative method of testing for the Rh factor. 2 and 3, Negative reactions: the inner light disc in 2 is due to slight convexity in the bottom of the tube. 4, Faintly positive reaction. 5, Weak reaction. 6 and 7, Typical positive reactions. (After Landsteiner and Wiener.) (Reproduced from the Journal of Experimental Medicine 74: 312, 1941. Magnification 1: 2.) (Weiner, A. S.: Am. Jour. of Clin. Path. 15: 106 (March) 1945.)

*checking by someone thoroughly familiar with the technic.*

The actual test is performed by mixing one drop of fresh 2 per cent suspension (in terms of blood sediment) of the blood to be tested with a drop of diluted anti-Rh serum in a small test tube. One having a diameter of 7 or 8 mm. is preferred. Incubates at 37.5° in a water bath. After the mixture has stood for one-half to one hour or when sedimentation has occurred, the sediment is examined, without disturbing it in the least, by the unaided eye. The uniformity of the sediment and its edges is marked in negative reactions; the positive reactions are characterized by an indefinite or even crinkled edge, and the body of the

swing in the centrifuge at low speed for one minute.

Three sera should be employed, namely, anti-Rh<sub>0</sub>, anti-Rh', and anti-Rh''.

The results may be interpreted as follows:

Anti Rh <sub>0</sub>	Anti Rh'	Anti Rh''	Designation of Types
—	—	—	Negative
—	+	—	Rh'
—	—	+	Rh''
—	+	+	Rh'Rh''
+	—	—	Rh <sub>0</sub>
+	+	—	Rh <sub>1</sub> (Rh <sub>0</sub> )
+	—	+	Rh <sub>2</sub> (Rh <sub>0</sub> )
+	+	+	Rh <sub>1</sub> Rh <sub>2</sub> (Rh <sub>0</sub> Rh <sub>0</sub> )

(After Weiner.)

For clinical work, standard anti-Rh<sub>0</sub> is usually sufficient; but, when reactions occur, the more detailed typing should be essayed.

Natural sensitivity to the Rh factors does not apparently occur. The sensitivity is acquired by either transfusion or in the pregnancy of an Rh negative woman bearing an Rh positive child. Fortunately, individuals differ in their ability to react to the Rh antigen so that according to Weiner only one negative person in twenty-five or fifty is apt to develop an intragroup hemolytic reaction or erythroblastotic baby. The various Rh factors also differ in their antigen properties. The Rh<sub>0</sub> factor is by far the most important clinically; so that Rh' and Rh'' people are clinically equivalent to Rh negative people because they lack Rh<sub>0</sub> and are therefore capable of producing anti-Rh<sub>0</sub> isoantibodies.

The subject is beyond a doubt a complicated and a difficult one—and by no means in a static phase. The observations of tomorrow may render obsolete the statements of today. Certainly blood grouping and the selection of donors for transfusion are not the task for poorly trained and inexperienced technicians. The practice of transfusing patients without a distinct indication is condemnable for this reason as well as for others. One hemolytic reaction calls for a very careful consideration of the blood type of the individual. Just so important is the consideration when several transfusions are anticipated.

The transfusion of a patient delivered of an erythroblastotic infant calls for the most careful investigation of blood type.

**The Demonstration of anti-Rh Agglutinin**—It is desirable to demonstrate the anti-Rh agglutinins in the serum whenever an intragroup hemolytic reaction follows a transfusion or whenever

a woman is delivered of an erythroblastotic baby. Even before birth the demonstration of these antibodies may anticipate the birth of a child with hemolytic anemia or erythroblastosis.

Diamond<sup>15</sup> has proposed a simple slide test which in his hands has been very successful:

#### *Procedure—*

Place 0.2 cc. of fresh oxalated Rh negative, Rh<sub>2</sub> and Rh<sub>1</sub> Group O blood or washed cells on an ordinary slide. If washed cells are employed a 50 per cent suspension is prepared.\* Mix with each of these 0.1 cc. of the serum to be tested. Warm the slide to 37° C. and rock or tilt the slide repeatedly. In positive reactions usually within one minute, and certainly within three minutes, agglutination may be seen in one or both of the Rh-positive sera. Thick suspensions must be employed or equivocal results will occur. Should the drop be too thick, or if rouleaux form, a drop of saline will remove the difficulty. Diamond facilitates rocking and warming by means of a small box pivoted over an electric light. A piece of ground glass in the top supports the slides under observation. If the specific types of cells are not available, the cells of the child and father may be employed if they are of the same Landsteiner group, or several Rh-positive bloods of the same Landsteiner group may be employed. The mother's cells or any other definitely known Rh-negative cells may be used as the Rh-negative control.

**Conglutination Test**—Weiner<sup>16</sup> has described this test to reveal the presence of anti-Rh agglutinins. Because of blocking antibodies, the classic cross matching tests fail to reveal all cases of intragroup incompatibility, that is to say, of the presence of Rh sensitization of the patient. Weiner believes that in the presence of blocking antibodies a third com-

\* It is a good plan in every laboratory to prepare a list of more or less permanent staff members whose blood types and subtypes have been determined by some capable person possessing the necessary diagnostic sera. These type cells are then available for such tests as the one here described, or in the case of rare types are available for transfusion.

ponent is necessary to bring about clumping of cells. The third component, according to Weiner, dissociates when plasma containing it is diluted with water (or saline). He, therefore, suggests suspending the test Rh positive cells in the individual's own serum or in inactivated AB serum. The patient's serum is used undiluted or diluted in inactivated AB serum. The test will be positive when this technic is employed where the patient's serum contains Rh agglutinins, or Rh blocking antibodies, or both. Weiner has found the presence of blocking antibodies of more serious import than Rh agglutinin without blocking antibodies, for in the former condition stillbirths are more apt to result. The occurrence of hemolytic phenomena several hours or days after birth he attributes to the delayed appearance of the third factor in the infant's plasma.

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## PEDIATRICS

*Edited by* WALDO E. NELSON, M.D.

## ANEMIA IN CHILDREN

C. R. RITTERSHOFER, M.A., M.D.

**Erythroblastosis Fetalis**

An excellent review of the present status of the Rh factor has been made by Potter.<sup>1</sup> The author includes an extensive bibliography of the subject.

The diagnosis of erythroblastosis fetalis has not always had the same meaning to all individuals. Macklin<sup>2</sup> has pointed out that erythroblastosis as originally defined indicated the presence of large numbers of nucleated red blood cells in fetal livers at a stage in development when erythropoiesis should be

largely absent from the liver. This situation is found in other conditions, other than those involving incompatible Rh factors in mother and fetus, such as diabetes in the mother, anoxemia, and hemorrhage in the fetus. Rh incompatibility is suggested as the term for the entity caused by a reaction between Rh antigens in the fetus and the specific antibodies in the maternal blood to combat them.

A diagnosis of proved Rh incompatibility in the living or dead infant can

be made when different Rh factors are demonstrable in mother and fetus, and when the antibodies against the infant's Rh positive red blood cells are found in the infant's serum.

Probable Rh incompatibility can be diagnosed in the living infant when different Rh factors are demonstrable in mother and fetus, and an anemia, or jaundice, or both unexplained by other conditions are present in the infant. The diagnosis is strengthened if other infants in the same family have suffered from fatal jaundice or from proved Rh incompatibility.

Probable Rh incompatibility can be diagnosed in the stillbirth or infant after death when different Rh factors are present in the mother and fetus, and when the fetal liver shows that hemolysis has taken place as evidenced by the presence of iron in the liver.

The diagnosis of Rh incompatibility may be suggested but should not be accepted as verified merely because the mother is Rh negative and the fetus is Rh positive. Erythroblasts in the fetal blood stream and in the fetal liver may be suggestive but are by no means diagnostic of Rh incompatibility, as they do not prove the presence of hemolysis but merely prove the increased need for red blood cells in the fetus.

Iron is not normally stored in fetal livers in such form that is demonstrable by the Prussian blue technic; therefore, iron as revealed by this test indicates excess blood destruction. One of the most frequent causes of such excess destruction is Rh incompatibility.

Polayes<sup>3</sup> reported six cases of erythroblastosis fetalis which resulted from isoimmunization induced by antigens other than Rh. As early as 1923 the possibility of interaction of the A and B agglutinin between mother and fetus with resultant pathologic processes was

suggested. After Levine revealed the mechanism of isoimmunization and the rôle which the Rh factor plays in the pathogenesis of erythroblastosis, it became apparent that the A and B antigens could induce isoimmunization with all its various pathologic effects in a manner similar to that of the Rh factors. In two of the cases reported, the mothers had Rh positive bloods in whom the possibility of isoimmunization by any of the variants of the Rh factor as well as by Hr was excluded. The diagnosis of erythroblastosis was established clinically as well as anatomically in one case. In each case the mother's blood was of group O, Rh positive, and the child's group A, Rh positive. In both cases the anti-A agglutinin in the mother's serum showed a high titer (1:700 and 1:750), a fact which strongly suggests isoimmunization of the mother with the A antigen of the baby.

A comparison of newborn infants with erythroblastosis fetalis with those born to diabetic mothers has been made by Miller, Johnson, and Durlacher.<sup>4</sup> Their study embraced the histories of 146 infants born to diabetic mothers in the Boston Lying-in Hospital, the New Haven Hospital, and the New York Hospital during a fifteen-year period. Of this number, 20 were included in this study since they were the only infants for whom there were data in the form of hematologic, Rh, or postmortem studies. Thirty-six infants made up the group with erythroblastosis fetalis.

It was noted that the changes occurring in both groups had many points of similarity, namely, an increased normoblastemia, extensive extramedullary erythropoiesis, a hypertrophy of the heart, hyperplasia of the islands of Langerhans, adrenal enlargement, edema, macrosomia, and a tendency to hemorrhage in all the tissues of the body.



The two most striking differences between the two groups of infants were that infants with erythroblastosis fetalis frequently have anemia and jaundice and the Rh factor in the mother's blood is negative, and that infants born to diabetic mothers rarely have anemia or jaundice and the distribution of the Rh factor in their mothers is similar to that in the population at large.

The following chart shows the distribution of Rh factor in the blood of diabetic mothers and mothers of infants with erythroblastosis fetalis.

<i>Mothers</i>	<i>Total</i>	<i>Rh+</i>	<i>Rh—</i>	<i>Not Determined</i>
Diabetic . . . . .	132	9	1	122
Erythroblastosis fetalis . . . . .	33	0	21	12

It has been held by Levine and his co-workers that the syndrome of erythroblastosis fetalis was dependent on isoagglutins developed in the mother during pregnancy. The authors contend that it is hard to reconcile this theory with the fact that about 10 per cent of the mothers are Rh positive, that in some mothers who are Rh negative no isoagglutinins can be demonstrated in spite of the fact that their infants have erythroblastosis fetalis, and that there is no correlation between the severity of the syndrome in the infant and the antibody content of the maternal serum. The authors believe that the data presented may show why the isoimmunization theory may not hold in all cases. Unless all infants without anemia and jaundice are excluded, some infants born to diabetic mothers will be included under the diagnosis of erythroblastosis fetalis. Infants born to diabetic mothers rarely have anemia or jaundice but do have large numbers of normoblasts in the peripheral blood and in the extramedul-

lary tissues and are similar to infants with erythroblastosis fetalis in many other important respects. The mother need not have symptoms or signs of diabetes at the time of the infant's birth but may develop them later in life. Numerically, the offspring of diabetic mothers are sufficient to account for the 10 per cent of infants whose mothers are Rh positive. The fact that the mother's blood is Rh negative is not an absolute answer to the question as to whether or not the infant will develop anemia or jaundice or both when normoblasts are present in large numbers in the blood. It is clear from the data that excessive extramedullary erythropoiesis can occur in the absence of anemia. This suggests that the erythropoiesis seen in the liver and other tissues of infants with erythroblastosis fetalis may not be dependent on the rapid hemolysis of the red blood cells.

Potter and Wilson<sup>5</sup> report the case of an Rh-negative woman who had previously given birth to a succession of infants with erythroblastosis and who was artificially inseminated with semen from an Rh-negative man. The result was the birth of a normal female infant whose blood was Rh negative. This seems further definite proof that fetal response to maternal immunity produced by the Rh factor is the fundamental cause of erythroblastosis.

Wiener *et al.*<sup>6</sup> have pointed out that blood transfusion is not the complete answer to the problem of the treatment of hemolytic anemia of the newborn, even when the infants appear to be in good condition at birth. *Transfusions* are merely a substitution therapy, and therefore save only those infants who would otherwise die from the extreme anemia brought about by the destructive action of the maternal antibodies. Some infants will not suffer a marked drop in

the amount of hemoglobin but still may succumb to the lethal effects of retaining the products of hemolysis in their bodies, a few die of hemorrhagic diathesis which does not appear to be influenced by simple transfusion of Rh negative blood, or by administration of *vitamin K*. It is theoretically possible that when an infant's blood is susceptible to the action of Rh antibodies, a complete *exsanguination transfusion*, entailing the removal of all but a small quantity of the infant's blood and its replacement by Rh negative blood at birth, or as soon thereafter as possible, may serve to prevent a lethal outcome.

Brandes and Cushman<sup>7</sup> suggest that (1) in the treatment of erythroblastosis

fetalis immediate recognition of the clinical entity with institution of appropriate therapy is necessary if survival is to be expected; (2) maintenance of external heat and oxygen is important during the critical period; (3) paternal Rh-positive blood is of no therapeutic value, but it is conceivable that father's blood may be instrumental in maintaining life until Rh-negative blood can be obtained; (4) since the Rh factor is present only in the cells and the presence of isoagglutinin is limited to the serum, it is safe to use the mother's red cells, after the plasma has been removed and the cells washed twice with sterile saline and resuspended in sufficient saline to make up for lost volume.

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## CHICKENPOX

ROBERT A. LYON, M.D.

Chickenpox occurring in newly born infants has been reported nine times in the literature and the patient observed by Oppenheimer<sup>8</sup> constituted the tenth case. The majority of such infants recovered, but in this last case death occurred six days after the onset of the illness. The mother, a nineteen-year-old Negro woman, developed chickenpox in the seventh month of pregnancy and five days

later delivered her infant which weighed four pounds at birth. On the fifth day of the infant's life, chickenpox lesions developed on various portions of the body and soon became contaminated with *Staphylococcus albus*. At autopsy, lesions were noted grossly in the liver, spleen, and intestinal tract but in the microscopic sections, all organs of the body were found to be affected.

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## DIGESTIVE SYSTEM

NINA A. ANDERSON, M.D.

**Mouth**—*Penicillin* has been used by Marks<sup>9</sup> in the treatment of severe or protracted cases of oral inflammations. Thrush of the mouth in a small infant responded to the topical use of penicillin in a dilution of 250 units per cc., but the effect was less rapid than when the drug

was injected intramuscularly in doses of 10,000 units at intervals of three hours up to a total of 40,000 units. Two patients with Plaut-Vincent's infection and one with herpetic stomatitis responded to penicillin given intramuscularly in doses of 20,000 units every three hours up to

a total of 100,000 units. There were no untoward reactions or manifestations in the cases which were treated with penicillin.

**Dental Caries**—In a group of fifteen boys and fifteen girls under forty-two months of age, Blatt, Kern, and Kortuem<sup>10</sup> found a marked variability in the per cent of salivary sugar. All of these children had good oral hygiene and had received an adequate diet. While the amount of glucose in the saliva may be related to the incidence of dental caries, it is noteworthy that in this group, in spite of comparatively large amounts of sugar in the saliva of some of the children, none of them had caries.

**Pyloric Stenosis**—The only entirely reliable roentgenographic sign of pyloric stenosis, according to Hefke,<sup>11</sup> is a narrowed prepyloric canal, 1.5 to 2.5 cm. long, corresponding anatomically to the narrowed lumen surrounded by the hypertrophied muscle. This finding can be demonstrated fluoroscopically as well as on films. When the pyloric opening time is delayed longer than five minutes, the presence of pyloric stenosis is considered likely. Less importance is attached to the emptying time of the stomach. Usually an infant two to four weeks of age will empty his stomach in two to four hours when 2 ounces of a barium mixture has been given. In a few cases, the thickened gastric wall can be demonstrated when the stomach is filled with air, but this sign is not helpful in the diagnosis. After the Ramstedt operation, the pyloric opening time becomes normal within a short time, but the deformity of the pylorus with its narrowing is still demonstrable for a considerable time. Rarely the esophagus shows some dilatation and even spasm at the cardiac end.

**Epidemic Diarrhea, Nausea, and Vomiting**—Although no age group is

immune, children of school age and young adults seem mostly to be affected with an epidemic disease characterized by diarrhea, nausea, and vomiting of unknown cause. Reimann, Hodges, and Price<sup>12</sup> have reported outbreaks of this disease similar to others previously reported and believe that it is a clinical entity. It has been suggested that a filterable virus is the cause and that the infection is air-borne, gaining entry through the respiratory tract or the gastrointestinal tract, mild nasopharyngitis being present in some of the patients. It is probable that the syndrome is a common one, often being overlooked or misdiagnosed. There are no characteristic laboratory data. The incubation period is short. The most common symptoms are abdominal discomfort, nausea, and diarrhea; and less frequently headache, a desire to defecate, vomiting, malaise, fatigability, shaking chills, anorexia, and fever. The average duration is 3.2 days and there are no complications. Characteristically, the disease is mild and requires no treatment. *Rest* in bed and local application of *heat* relieves the abdominal discomfort, and limitation of *diet* controls the nausea. Headache and general body aches respond to *acetylsalicylic acid* or *codeine*. Only the most severe cases require intravenous administration of 5 per cent *glucose* solution, but in such instances the improvement is striking.

**Diarrhea**—Neter<sup>13</sup> has called attention to the presence of various proteus and paracolon bacilli in the feces of infants under one year of age who have neither history nor evidence of diarrheal disease. Among fifty healthy infants, the rectal swabs of seventeen (34 per cent) contained solely members of the bacillus coliaerogenes group, and thirty-three (66 per cent) of the fecal specimens harbored various other enteric micro-

organisms as well. Various proteus bacilli were encountered in twenty (40 per cent) of the stools which were examined. Paracolon bacilli were recovered from eleven (22 per cent). Salmonella-Shigella agar was found to be more efficacious than any of the other culture media used.

Neter and Clark<sup>14</sup> isolated paracolon bacilli from the feces of forty-nine patients, thirty-nine of whom had diarrhea, six had a history of diarrheal disturbance without evidence of it at the time of examination, and four presented neither history nor evidence of diarrhea. Twenty-five of the patients with diarrhea had no pathogenic or potentially pathogenic enteric bacilli other than members of the paracolon group, and the remaining fourteen had other enteric micro-organisms, namely, paratyphoid or dysentery bacilli, *B. proteus*, or *B. morganii* type I. Six of the infants were hospitalized solely on account of the diarrhea, while the other nineteen had such diseases as upper respiratory infection, otitis media, pertussis, septicemia, or impetigo.

Among twenty-one cases of salmonella enterocolitis in infants and children, Neter and Clark<sup>15</sup> found *S. typhi* murium in eleven infants less than a year and a half of age who had diarrhea. In the other ten patients, who ranged in age from three weeks to twelve years, the enterocolitis was caused by other Salmonella organisms. Of the entire series, eighteen recovered and three died. In several instances, salmonella enterocolitis developed in patients suffering from or recuperating from other illnesses, such as meningococcic meningitis, beta streptococcic bacteremia, and bronchopneumonia, but it was difficult to ascertain whether these infections rendered the patient more susceptible to Salmonella infections. **Sulfonamides** were given to some of the patients, but whether

their use contributed to recovery could not be stated. In some of the cases, the organisms persisted in the intestinal tract in spite of the administration of a sulfonamide.

Varela<sup>16</sup> has reported symptoms resulting from Salmonella infection ranging from mild diarrhea of short duration to the severest form of cholera-like prostration. In the center created for the study of Salmonella infection in Mexico City, 89 (8.1 per cent) of 1101 stool specimens of children with diarrhea examined during the year 1942-1943 were found to contain Salmonella organisms, 90 different strains being isolated. The greatest incidence of Salmonella infections was found in children between the ages of one and two years and during the months of the highest temperature. **Sulfaguanidine** was not effective in ridding the intestinal tract of the various strains of Salmonella organisms.

**Congenital Alkalosis with Diarrhea** — Gamble, Fahey, Appleton, and MacLachlan<sup>17</sup> have described a case of congenital alkalosis with diarrhea in which there was a decrease in the plasma chloride, marked excess of chloride over sodium in the stools, and barely measurable amounts of chloride in the urine. The pH of the stools was more acid than that of the urine. The voluminous watery diarrhea began at birth. No reduplication or diverticulum of the intestinal tract was found on surgical exploration, and careful search at autopsy failed to reveal aberrant gastric mucosa. Although the infant presented an uncompensated alkalosis, there were no discernible signs of tetany at any time. The findings seemed to indicate an intrinsic defect in the control of electrolyte distribution in the body fluids. An elevation of plasma chloride was obtained by increasing the intake of sodium chloride but at the cost of a huge increase in the volume of the

stools. An elevation of plasma chloride also occurred on the first day of therapy with *ammonium chloride*, but on the second and third days the greater part of the intake was lost through the increased stool volume. Subcutaneous infusion of 0.9 per cent sodium chloride solution resulted in a large positive balance of sodium with twice as large a retention of chloride; almost no chloride was excreted in the urine, the greater portion of it as well as of sodium being excreted in the stools. An intensely alkaline urine resulted from the disproportionate excretion of sodium in relation to chloride by the kidneys. An increase in stool volume paralleled the fecal excretion of chloride.

It was found that the administration of *sodium chloride* solution subcutaneously for the elevation of plasma chloride had to be spaced at intervals of several days in order to keep the diarrheal disturbance at a minimum.

Darrow,<sup>18</sup> in performing metabolic studies on a similar case, noted that, since chloride was lost more rapidly than sodium, extracellular sodium was transferred into intracellular fluids with approximately equivalent amounts of potassium being released from the cells and excreted. He believes that the correction of severe alkalosis by the administration of sodium chloride cannot be entirely successful as long as a deficit of potassium persists. Insufficient sodium was retained from the administration of sodium chloride and potassium chloride to account for the increase of extracellular chloride, but retention of potassium accounted for the release of sufficient sodium from the cells to replace the deficit of extracellular sodium and to explain the changes in concentration of extracellular electrolytes.

**Abdominal Pain**—Ratner<sup>19</sup> emphasizes that food allergy may be an etio-

logic factor of abdominal pain in children. The abdominal pain may occur with or without other allergic manifestations, such as urticaria or asthma, but, as a rule, there are other gastrointestinal symptoms, such as diarrhea, flatulence, mucous stools, nausea, vomiting, or even constipation, which follow the ingestion of a particular food. If the symptoms are limited to the gastrointestinal tract, protein skin tests may be negative, and the diagnosis must rest on careful historical data relative to the ingestion of certain foods or on the reproduction of the clinical pattern by ingestion of the suspected food. When associated with urticaria or asthma, the skin tests are usually positive. An eosinophilia is rarely present except in chronic cases. If the abdominal pain is severe and the possibility of an acute surgical condition cannot be eliminated, *laparotomy* may be indicated. When allergy is the cause of the pain, relief may be obtained at times from a subcutaneous injection of *epinephrine*, *ephedrine sulfate* by mouth, or *atropine* or its derivatives orally or subcutaneously. Roentgenographic findings include pylorospasm, delayed emptying of the stomach, and hypertonicity and hyperperistalsis of the intestine. The treatment of the acute episode, in addition to the subcutaneous administration of epinephrine, followed by the oral use of atropine, *belladonna*, or *syntropan*, includes sedation which should be continued for a few days after the acute episode. The offending food should be eliminated from the diet and subsequently reintroduced in small amounts in a well-cooked state until a tolerance is gradually established.

In the diagnosis of conditions causing abdominal pain, Brennemann<sup>20</sup> emphasizes that palpation is the most revealing procedure for eliciting pain and tenderness. Pain resulting from obstruction is

intermittent and associated with very little tenderness, pressure often being a source of relief from pain. In conditions resulting from infection, the pain is more constant and uniform unless there is concurrent obstruction, and tenderness is always present over the affected area and is more pronounced than unelicited pain.

There are many conditions to be considered in making the differential diagnosis of abdominal pain in children. Strauss<sup>21</sup> lists acute enterocolitis, intussusception, mesenteric adenitis, acute inflammation or rupture of Meckel's diverticulum, congenital intestinal anomalies, infections, ovarian cyst, rupture of Graafian follicle, gallbladder disease, congenital megacolon or Hirschsprung's disease, subacute and chronic ulcerative colitis, strangulated hernia, and exanthematous fevers. An early diagnosis of appendicitis is important in children because the appendix ruptures sooner and is more likely to produce generalized peritonitis than in the adult. The author's conviction is that early operation is the most important factor in securing good results and a low mortality rate.

**Regional Ileocolitis**—Sprague, Anderson, and Aaron<sup>22</sup> observed a fifteen-year-old girl who had fever of long standing, an elevated sedimentation rate, and tenderness in the right side of the abdomen without other identifying symptoms until she developed recurring perianal abscesses without obvious cause, which subsequently were found to stem from infection extending down through the pelvic tissues. The observation of these abscesses led to investigations which indicated the proper diagnosis of regional ileocolitis. A barium enema suggested an inflammatory infiltration of the terminal ileum, the cecum, and the ascending colon. The diagnosis was confirmed at operation, and after resec-

tion of the diseased bowel and lymph nodes a side-to-side ileocolostomy was performed. The patient made a good recovery.

**Chronic Intussusception**—Chronic intussusception in children is uncommon and the diagnosis is seldom obvious. Weeks or months may elapse before the true nature of the condition is suspected, or it may be revealed only by operation or at autopsy. Based on their observations of three cases of chronic intussusception, Garvie and Kemp<sup>23</sup> recommend thorough roentgenographic studies with a barium enema in instances in which the patient has had repeated attacks characterized by sudden onset of griping central abdominal pain. Other symptoms may be absent or unreliable. The tumor may be missed in the physical examination because of the difficulty in obtaining relaxation of the abdomen, and examination under anesthesia should be considered. In about 5 per cent of the cases, the intussusception is of the enteric variety and, in such instances, is not revealed by the barium enema, but the preliminary films of the abdomen may show abnormal gaseous distention of a coil or coils of small bowel and the diagnosis can be confirmed by a barium meal.

**Congenital Megacolon**—Highly favorable results were obtained in seven of the patients on whom left lumbar sympathectomy was performed by Penick.<sup>24</sup> Three were greatly improved but occasional cathartics or enemas were still required. The eleventh patient, however, in whom there was involvement of both colon and ileum and for whom spinal anesthesia had had little effect preoperatively, was not benefited by the procedure. Follow-up roentgenographic studies of four patients showed less dilatation and retention than at the time of the original studies. The plan of management which

the author proposes is: Adequate observation and study of the patient for the diagnosis, therapeutic test with acetylcholine or a spinal anesthesia, and surgical treatment not contemplated until medical management utilizing the sympathetic stimulants has had a trial of eight to ten weeks. The author does not advise operation upon any patient less than two and one-half years of age unless it is a lifesaving measure. Unilateral sympathectomy should be tried before resorting to more radical procedures, and it is advised if spinal anesthesia produces a copious bowel movement and medical regimen has not proved highly satisfactory. Bilateral ganglionectomy should be contemplated only if there is no improvement after left lumbar sympathectomy, and intestinal resection only if all of these have failed.

**Rectum**—Lee<sup>25</sup> has reviewed and studied sixteen cases with congenital anomalies of the lower part of the rectum, of which two had incomplete rupture of the anal membrane, two had congenital stenosis of the anus and the lower part of the rectum, eleven had imperforate anus with the rectal pouch a closed sac and separated from the anal membrane, and one had an imperforate anal membrane, stenosis of the anal canal, and a normal rectum separated from the sigmoid flexure by a membrane. Eleven of the patients in the series had fistulas and eleven also presented associated anomalies other than fistulas.

The symptoms and signs were those referable to the obstruction including refusal to nurse, persistent vomiting, and abdominal distention, the absence of an anal opening and failure to pass meconium, or passage of it from an abnormal exit, such as the vagina, the urethra, or a perineal fistula. Roentgenographic and fluoroscopic study of the abdomen and

pelvis of the infant, in an inverted position with an opaque marker in the anal dimple or at its usual site, was effective in outlining the rectal pouch by the displacement of gas into it. Barium sulfate or iodized oil was also injected into the distal loop of the intestine to facilitate accurate localization and as an aid in tracing fistulous communications.

The treatment varied with the type of anomaly and the age of the child. Repeated dilatation of the stricture with dilators of various types or with the finger was usually adequate to overcome a stenotic obstruction which was not more than 1 to 4 cm. above the anus. When the opening in the anal membrane was small, the obstruction could be relieved by a cruciate incision followed by dilatation. Simple cruciate incision of the membrane followed by regular dilatation was also effective in correcting imperforate anus due to a persistent anal membrane.

Immediate mobilization of the rectal pouch and proctostomy by the direct perineal approach was the treatment of choice when the rectal pouch was readily accessible. Otherwise, a colostomy in the transverse colon was necessary with a plastic repair of the perineal region being performed three or four years later. If the rectal pouch was high in the pelvis, preliminary colostomy was often necessary; but if the obstruction was membranous, incision and dilatation from below might be sufficient.

The authors recommend that fistulas be left undisturbed during infancy. They stress the need for careful training to overcome the anal incontinence which may follow the reconstruction.

**Tumors**—In a review of five cases of lymphosarcoma of the bowel in children under twelve years of age, Cutler, Stark, and Scott<sup>26</sup> observed two of the lymphocytic variety, two of the lymphoblas-

tic, and one of the reticulum cell group. The youngest patient was four months of age and the oldest seven years. All were boys. Intussusception occurred in three of the five patients. The youngest in the series had classic symptoms of acute intussusception and, at operation, was found to have one of the ileoileal type whose leading point was an intramural lymphosarcoma. Two patients had increasing constipation for three and four months, respectively, leading to fecal impaction. One of these patients developed acute intestinal obstruction a few days after hospitalization and, by barium enema, was found to have an ileocolic intussusception associated with a large tumor of the terminal ileum; the other patient had a chronic colocolic intussusception resulting from lymphosarcoma of the cecum and ascending colon. The fifth patient presented an essentially asymptomatic irregular abdominal mass filling the right lower quadrant of the abdomen and attention was attracted by bloody stools. Two of the patients developed the blood picture of lymphoblastic leukemia, during the terminal stage. In the opinion of the authors, a combination of radical surgical *extirpation* of the involved bowel and mesentery followed by heavy *roentgen ray therapy* to the abdominal and mediastinal drainage areas is the treatment of choice. One patient in this series survived and has no evidence of recurrence during the fifteen months since the abdominoperineal resection of the rectal tumor.

**Liver**—Following catarrhal jaundice, Salmon and Richman<sup>27</sup> found persisting liver damage, as measured by the cephalin cholesterol flocculation test and the lowering of the diastatic activity of the serum, which persisted for a period of a few weeks to several months following apparent clinical recovery. Among the sixteen cases studied, in fifteen instances

the cephalin cholesterol flocculation test remained positive for three weeks to seven months after the return of the icterus index to normal. The patients had neither subjective nor objective manifestations suggestive of hepatic insufficiency during the period of observation following the subsidence of the jaundice. The results of the bromsulfalein dye test in nine of the sixteen cases paralleled the icterus index. Intravenous hippuric acid tests in four of the sixteen cases yielded results roughly in proportion to the height of the icterus index.

McFarlane and Branday<sup>28</sup> have observed eighteen cases of chronic hepatic enlargement with ascites in which the etiology was unknown. Onset with fever, then painless enlargement of the abdomen, frequently loss of appetite, nausea and vomiting, and irregularity of the bowels were the symptoms. There was wasting of the arms and the legs, a drawn facies, and a slight jaundice. The sedimentation rate was increased; there was a moderate anemia, leukocytosis, and low plasma protein; and the urinalysis, the blood sugar, and the blood urea were normal. *Paracentesis* gave temporary relief, and a balanced and generous *diet* and better hygienic conditions produced marked improvement in some instances. Some of the patients responded to the administration of *dried yeast* and one to *glycocoll*.

**Celiac Syndrome**—Further evidence of a genetic factor in fibrocystic disease of the pancreas has been supplied by Howard,<sup>29</sup> who has observed two proved cases and a third possible one in children of the same family. There were three living children who were free from symptoms of the disease. There had been seven infantile deaths in the paternal grandmother's family, the etiology of which was not established, but there was no suggestive evidence of the dis-



ease among twenty-five cousins in the maternal family. The familial occurrence suggests a heterozygous inherited factor.

In a series of ten male and four female infants with fibrocystic disease of the pancreas, Baggenstoss and Kennedy<sup>30</sup> noted a mean age at the time of death of 8.7 months. One of the infants died at five days of age from meconium ileus. In eight patients, with a mean age at death of 7.4 months, the respiratory symptoms of cough and cyanosis predominated over those of the gastrointestinal tract. Five of the patients, who had many signs and symptoms of celiac disease but failed to respond to accepted dietary treatment, died at a mean age of fourteen months, also as a result of the pulmonary infection. There were few grossly recognizable pancreatic changes, but microscopically there were varying amounts of pancreatic fibrosis and dilatation of the acini and ducts. Death resulted from suppurative bronchitis, bronchiectasis, patches of bronchopneumonia, and abscesses, except in the instance of meconium ileus. The bronchi and their glands usually contained an exudate that was more purulent than mucoid but occasionally the bronchial glands were distended with mucous secretion. Fatty metamorphosis of the liver was present in seven cases. Distention of the glands of the duodenum with mucus was observed in nine cases, but there were no similar changes observed in any other portion of the gastrointestinal tract. Calcium salts were present in the cells of the convoluted tubules, in Henle's loops, and occasionally in the cells of the collecting tubules, but the significance of this finding is unknown though the authors are of the opinion that it might indicate some disturbance in metabolism or excretion.

Philipsborn, Lawrence, Gibson, and Greengard<sup>31</sup> have quantitatively ana-

lyzed the duodenal drainage of infants with steatorrhea for enzymatic activity and determined the volumetric response of pancreatic excretion to secretin or N/10 HCl. Studies were performed on normal children, children considered "feeding problems," children with fibrocystic disease, and children with celiac disease. These authors believe that an estimate of the tryptic activity in the duodenal drainage is the most reliable index of pancreatic function and that values of less than 4 gm. of liberated nitrogen per 100 cc. of duodenal fluid are abnormal in children. A diminished output of one pancreatic enzyme is usually accompanied by a similar change in the output of the others. Examination of the clearest specimen of the highest pH from each child minimized the dilution of the pancreatic fluid by the succus entericus, bile, and stomach contents. Less than 0.5 gm. of liberated dextrose per 100 cc. of duodenal drainage is abnormal during the first twelve months of life; subsequently, less than 2 gm. of liberated dextrose is abnormal in children. When less than 60 cc. of N/20 NaOH is required to neutralize the free fatty acids produced by the lipolytic activity of 100 cc. of duodenal fluid, the pancreatic lipase may be considered diminished in children. The enzymatic activity in the duodenal drainage is markedly diminished in fibrocystic disease; it remains essentially normal in celiac disease. The response to intravenous secretin or intraduodenal N/10 HCl is reduced in fibrocystic disease but may remain normal in celiac disease. "Feeding problems" with some degree of malnutrition showed a marked hypochylia pancreatica, possibly on the basis of temporary pancreatic insufficiency.

Paterson, Pierce, and Peck<sup>32</sup> noted gains in weight and height and improvement in general health in the early weeks

of treatment of twenty-six cases of idiopathic celiac disease and of four cases of the secondary type of disease, resulting from chronic foci of infection, with parenteral *liver extract* and *vitamin B* complex given parenterally or orally. This improvement was sustained over a period of months in patients who received sufficiently intensive and prolonged therapy. Less dramatic improvement was obtained when oral vitamin B complex preparations were used. Children took and thrived on normal balanced diets, including uncooked fat (milk, butterfat) during or after the initial weeks of treatment. The total amount of fat in the stool decreased in all but four cases. There was slower improvement when the patient had upper respiratory infection, and improvement of the chronic infection hastened the improvement in those who had "celiac syndrome" of the secondary type. None of the vitamin A absorption curves returned to normal, but some of the oral glucose tolerance curves returned to normal after treatment.

Based on the study of twenty-six cases of cystic fibrosis of the pancreas, Philipsborn, Lawrence, and Lewis<sup>33</sup> have concluded that the diagnosis could not be determined by a "characteristic" stool and particularly not by a single stool specimen, since there was an extreme variety of stools which had frequently changing properties, apparently dependent upon variations in the enzymatic and absorptive power of the gastrointestinal mucous membrane as well as on the motor activity of the bowel and the type of bacterial flora present. These authors feel that serial vitamin A absorption curves are of practical value in the diagnosis of this condition.

Andersen<sup>34</sup> has pointed out that the large foul foamy stools of the patients

with celiac disease may or may not contain a relative excess of fat, while the fatty stools of the patient with pancreatic deficiency may appear normal. The naked eye diagnosis of a fatty stool is, therefore, unreliable. Quantitative determinations of fecal fat from a controlled diet are required, and they must be compared with control determinations for comparable subjects. The absolute figures for daily excretion of neutral fat are more informative than relative ones; the unsaponifiable fraction and hence the neutral fat fraction are constantly present and remain above a certain minimum level, and they may form a large proportion of fecal fat if absorption of glycerides and fatty acids is good but only a small proportion if absorption of dietary fat is poor. Patients with pancreatic deficiency and absence of pancreatic lipase from the duodenal juice may have fatty stools which, on analysis, give low values for neutral fat. The failure to find an excess of neutral fat by analysis of the feces does not disprove the diagnosis, but high values for neutral fat are significant. Neutral fat is hydrolyzed *in vitro* when feces stand at temperatures as low as 43° to 44° F. (6° to 7° C.).

The determination of total daily fecal excretion of fat is of real importance in the clinical study of chronic indigestion. For children under the age of six years, excretion of more than 50 gm. wet weight or 13 gm. dried weight is beyond the limits of normal. In the age group of two to six months, the total stool is smaller with a relatively greater amount of fat and a smaller proportion of neutral fat than for the older age group. Microscopic examination of feces for fat is a method useful for the screening out of patients with steatorrhea.

In a study of patients of various ages with congenital pancreatic deficiency

while on a normal diet, Andersen<sup>35</sup> found that the total fecal excretion was within normal range for three patients under the age of six months but was excessive for older infants and children and that the fecal excretion of fat was excessive for all of the patients. The stools were usually formed and of normal appearance but had a distinctive and penetrating odor. The characteristic stool was not loose, watery, nor foamy. The amount of fecal fat was decreased when the amount of dietary fat was reduced and the decrease was roughly proportional. The amounts of fecal fat and the total fecal excretion were usually reduced when pancreatin was administered. In balance studies performed on two patients with congenital pancreatic deficiency, the addition of fat increased the excretion of feces, protein, fat, and ash. Corn oil, an unsaturated fat, and butter, a saturated one, were about equally well utilized. Adequate retention of protein was obtained only with diets deriving 21 per cent or more of their calories from protein. Carbohydrate was better utilized in the form of cereal starch than in the form of banana. No great difference was observed in the utilization of bread and oatmeal as compared with that of potato and oatmeal. Starch and sugar were well tolerated. A definite statement as to the optimal diet must be deferred until enough balance studies have been done, but it is suggested that, for patients with congenital pancreatic deficiency, protein should provide 25 per cent of the calories, the proportion of fat should be small but should include eggs and fat-soluble vitamins, and carbohydrate should be provided in part as sugar and for older infants and children, in part in the form of cereal, starches, and potato if these foods are tolerated. The total

caloric intake should be sufficiently high to satisfy hunger and to allow gain in weight. *Pancreatin* should be given and also supplemental *vitamins A* and *D* since a diet low in fat may be deficient in them. *Vitamin B* complex is also given, with less clear indications.

Recommendations for dietary therapy have been made by Andersen,<sup>36</sup> based on observations in thirty-eight patients with congenital pancreatic deficiency, of whom seventeen are still alive. The major rôle played by infection of the respiratory tract, with respect not only to survival but to all of the disabilities associated with the disease, is recognized, and *penicillin* is indicated and has produced response of the respiratory symptoms in certain patients.

A *low fat, high protein diet* (6 gm. of protein per kilogram of body weight per day) is recommended, with a liberal allowance of vegetables, fruits, and sugar, and a moderate restriction of starch, supplements of vitamin A, pancreatin, and vitamin B complex. Representative diets for patients with pancreatic deficiency follow:

A. Patients under the age of one year: 150 (120-180) calories per kilogram of body weight.

*Breakfast:*

- 3-4 ounces (90-120 cc.) of fruit juice (orange, grapefruit, or tomato) or puréed fruit.
- 1 egg, soft cooked.
- 1 slice of zweiback (may be garnished with jelly).
- 1 mashed ripe banana if appetite is good.
- 6-8 ounces (180-240 cc.) of formula.
- 1 level teaspoon of pancreatin (1.5 gm.).

*Dinner:*

- 1-2 tablespoons or more of minced lean meat, broiled, boiled, or roasted only.
- 1-2 tablespoons or more of puréed vegetable.
- 1 slice of zweiback (optional).
- Dessert: puréed, cooked, or canned fruit, gelatin, or junket made with skim milk.
- 6-8 ounces of formula.
- 1 level teaspoon of pancreatin.

*Supper:*

1-2 tablespoons of pot cheese or meat; the pot cheese may be flavored with honey, jelly, or banana powder.

1-2 tablespoons or more of puréed vegetable.

Dessert, zweiback, formula and pancreatin as at noon.

*Evening:*

6-8 ounces of formula.

Formula: Calculate to provide two thirds of total calories.

Protein milk to provide three fourths of formula calories.

Banana powder to provide one fourth of formula calories.

Vitamins: Concentrate of vitamins A and D sufficient to provide 20,000 U.S.P. units of vitamin A per day, given in two or three doses.

Vitamin B complex.

Ascorbic acid, 0.05 gm., if fruit juice is not well taken.

B. Patients aged one to two years: 150 calories per kilogram of body weight. A trial with skim milk is made soon after the twelfth month for patients who are doing well; it is usually well tolerated. Fish is tried next. One small serving of starch per meal is added. The transition to the diet for older infants is made gradually.

C. Patients aged three to four years and older.

*Breakfast:*

Fruit or fruit juice.

$\frac{1}{2}$  to  $\frac{2}{3}$  cup cooked whole grain cereal with skim milk and sugar.

1-2 eggs, prepared in any way except fried.

$\frac{1}{2}$  to 1 slice of bread or toast, preferably whole-grained, with jelly, honey, without butter.

1 or more glasses of skim milk, may be flavored with sugar, cocoa, vanilla, etc.

1 level teaspoon of pancreatin.

*Dinner:*

Large serving (3-4 teaspoons or more) of lean meat, poultry, or fish; broiled, boiled, or roasted, all visible fat to be cut off.

3 or more tablespoons of cooked vegetable.

1 small serving of starch, as potato, rice, or macaroni.

1 or more glasses of skim milk.

Dessert: cooked or canned fruit, gelatin, junket made of skim milk, custard, puddings, or sponge cake.

1 level teaspoon of pancreatin.

*Lunch or supper:*

Same as dinner, except that pot cheese may be substituted for meat.

*Between meals:*

Any food item included in this list, except starch.

Hard candy, sponge cake, and arrowroot biscuit may be given.

Note—The child may receive second portions of any item except starch. Any of the allowed foods may be served in the form of soup or frozen desserts, if desired.

Vitamins: Same as those given the first year.

*General Instructions—Rules for parents:*

1. Include only the foods on the list.
2. Do not serve raw vegetables and fruits other than orange, grapefruit, apple, banana, pear, peach, and lemon juice.
3. Do not use any packaged food of which you do not know the ingredients or which contains substances not on the allowed list.
4. Do not use flour, cornstarch, etc., in the preparation of food without reducing the feeding of starch.
5. Remove all visible fat on meats; broil, boil, or roast only.
6. Do not use fats or oils of any kind in the preparation of food.
7. Use only milk which is commercially skimmed. It is not enough to pour the cream from the top of a bottle of whole milk. Use 1 quart (1 liter) daily.

The valid criterion of successful therapy is the control of infection of the respiratory tract and continued health of the patient. Patients who survived the first year of life gained slowly during the first year; during the second year, growth often continued at a steady rate so that by the age of two years the weight was near or within the normal range. Survivors over the age of two years, whether treated or untreated, have

## FOODS ALLOWED

<i>Meats</i>	<i>Vegetables</i>	<i>Fruits</i>
Beef	Tomato juice	Strained orange juice
Lamb	String beans	Pineapple juice
Veal	Squash	Grapefruit juice
Liver	Carrots	Grape juice
Kidney	Peas	Lemon juice
Chicken	Asparagus	Lime juice
Turkey	Cauliflower	Juice of berries
Fish	Beets	Bananas
Shellfish (oyster, clam, shrimp, crab, lobster)	Spinach	Scraped or peeled apples, pears, and peaches
	Mushrooms	Cooked or canned apples, apricots, pears, peaches, pineapple
	Onions	Strained cranberry juice
	Beet greens	
	Eggplant	
	Broccoli	
<i>Starches</i>	<i>Miscellaneous</i>	
One serving per meal only	Egg	
Bread, preferably whole-grained	Pot cheese	
Potato, rice, noodles, macaroni, spaghetti	Soup without fat	
Lima beans, if potato, etc., is omitted	Jelly or jam without seeds	
Split peas, if other starch is omitted	Marshmallows	
	Sugars—white sugar, brown sugar, corn syrup, honey, maple sugar, molasses	
	Lollipops or hard candy	
	Fruit ices	
	Cake without fat—sponge, angel food	
	Gelatin	
	Cocoa	
	Junket	
	Custard, including frozen foods	

## FOODS NOT ALLOWED

<i>Meats and Fats</i>	<i>Miscellaneous</i>
Butter, oleomargarine	Raw vegetables or fruits not on list
Fat meats, bacon, pork	Luncheon meats, salami, etc.
Lard, Crisco, Spry	Cream candies, chocolates
Fried foods	Crackers
Cream, whole milk	Cookies, doughnuts, pie
Peanut butter	Gravy with fat or flour
Cheese other than pot cheese	Corn
Chocolate	Beans—navy or kidney
Salad oils, olive oil, mayonnaise	Cake containing fat
Duck or goose	

For older children add the following, if trial shows toleration:

Salads, melons, berries, small amounts (1 teaspoon) of peanut butter, a few nuts, preferably as flavoring.

weights and also heights which are usually in the lower part of the normal range. When therapy was begun before or immediately after the onset of the cough, the cough failed to appear or soon disappeared and no further bronchitis developed as long as the patient remained on the regimen. When a chronic cough was present but suppurative bronchitis was not, growth was somewhat delayed but there was gradual improvement in the cough. When dietary therapy was begun after the chronic cough was complicated by purulent staphylococcic bronchitis, there was sometimes a temporary gain in weight, and possibly some prolongation of life, but the fatal outcome was not averted.

Administration of pancreatin alone or in combination with vitamin A did not

prevent bronchopneumonia. A low fat diet alone permitted the prolonged survival of several patients with late onset of the disease, but the nutrition and the status of the infection of the respiratory tract were improved only by institution of the complete regimen. Diet and vitamin A seemed to exert a greater influence than the administration of pancreatin. Dietary therapy seemed capable of preventing special susceptibility to infection, and some patients who remained free from fresh infections over long periods gradually lost the chronic cough. When the regimen was relaxed for several months, further infection of the respiratory tract followed. It appears probable, therefore, that the dietary therapy needs to be continued throughout life.

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## DIPHTHERIA

ROBERT A. LYON, M.D.

Diphtheria in young infants is uncommon. It has been supposed that the newly born infant has an immunity transmitted *in utero* from the mother which protects him during the first weeks of life. In the studies of Wright and Clark,<sup>37</sup> the incidence of positive Shick reactions among parturient women varied from 46 to 57 per cent. The incidence of positive reactions was greater in the younger mothers than in those over thirty-five years of age. When small amounts of toxoid were administered to these patients, the antitoxin levels in the blood generally rose rapidly. It seemed probable, however, that, unless such a procedure was carried out, the amount of antitoxin transferred to the newborn was small in the majority of cases. When the infant was Schick-tested, the results agreed with those of the mothers

in 84 per cent of cases. In the presence of severe epidemics of diphtheria, the need for providing more complete *immunization* for the young infant seemed apparent. Either active immunization could be started at the age of a few weeks, at which time the infant's antigenic response is not always satisfactory, or the mothers could be given injections of toxoid during the latter months of pregnancy to stimulate a rise in blood antitoxin which would be transferred in part to the fetus.

The effectiveness of diphtheria immunization in a community in which severe forms of the disease had occurred has been analyzed by Grant.<sup>38</sup> Among 12,289 children under fifteen years of age who had received complete courses of immunization, 0.75 per cent developed diphtheria but none died. Among 14,536

children who had had the disease previously or who had insufficient or no immunization, 1.1 per cent developed the disease and 11 per cent of this group died. The immunized patients frequently did not maintain blood antitoxin levels adequate to protect them from the infection but responded quickly to the invasion of the bacteria and escaped severe forms of the illness. If an epidemic of diphtheria is caused by mild strains of the bacillus, the incidence of the disease will probably be lowered considerably by immunization procedures, but in the epidemics resulting from gravis strains of the organism, the preventive inoculations will probably only reduce the severity of the infection without affecting the rate of incidence.

Further evidence that monthly intervals between injections of diphtheria toxoid are more effective than weekly or biweekly intervals has been gathered by Bousfield.<sup>39</sup> Positive Schick tests were converted into negative reactions in 96 per cent of cases when a month elapsed between injections. With shorter periods between treatments, the conversion from positive to negative reactions occurred in from 83 to 94 per cent of cases.

Combined immunization against diphtheria, tetanus, and whooping cough has been carried out by Hamilton and Knouf.<sup>40</sup> The material consisted of fluid tetanus and diphtheria toxoid to which pertussis vaccine was added so that there were forty billion pertussis organisms per cubic centimeter in the mixture. Three injections were given to sixty-four children in doses of 0.5 cc., 1 cc., and 1 cc., subcutaneously at intervals of four weeks. The reactions were very slight and no serious symptoms developed. Measurement of pertussis agglutinins and tetanus and diphtheria antitoxin titers indicated that there was adequate

response in the majority of instances about three weeks after completion of the course. It was questionable how long the immunity persisted.

The type of mixture of whooping cough vaccine and diphtheria toxoid which is most satisfactory has been studied by Sauer, Tucker, and Markley.<sup>41</sup> When standard fluid diphtheria toxoid was given (simultaneously but not mixed) with pertussis vaccine, intervals of three weeks between injections seemed most satisfactory. When tested six weeks after completion of the course, 97 per cent of the patients were Schick-negative and 97 per cent had adequate complete fixation tests for pertussis. Standard diphtheria mixed with pertussis vaccine resulted in negative Schick tests in 97 per cent and adequate complement fixation reactions in 72 per cent. A subsequent dose of pertussis vaccine raised the level of antibodies satisfactorily in the group who were not sufficiently protected against the disease. When alum-precipitated diphtheria toxoid was mixed with pertussis vaccine, 98 per cent of the patients became Schick-negative and 92 had satisfactory complement fixation reactions to pertussis. There were more severe reactions with this material. Two per cent of this group of patients developed sterile abscesses. The authors likewise demonstrated that immunity responses were much better when the patients received their injections three or four weeks apart than when the intervals were shorter.

Protamine diphtheria toxoid has been developed by Ross.<sup>42</sup> The addition of protamine sulfate to the diphtheria toxoid precipitated a large proportion of the bacterial protein leaving in solution the antigenic material. When this toxoid was used in animal tests and in human patients, the rise in antitoxin levels and

the reversal of positive Schick tests to negative were satisfactory. A series of 2600 children was adequately immunized with 1 cc. of the toxoid and their reactions were very mild, not a single child becoming ill. When the material was administered to adults, the reactions were generally mild, although there were three patients who were definitely sen-

sitive to the diphtheria toxoid and reacted with slight elevations of temperature for a short period of time. Although the number of adults tested was still small, it seemed probable that this type of diphtheria toxoid might be a good immunizing agent for the older patient and others who are apt to react severely to the antigen.

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## THE GENITOURINARY TRACT

WILLIAM BUTSCHER, M.D.

### Acute Glomerulonephritis

**Treatment**—Early recognition of acute hemorrhagic glomerulonephritis is the most important factor in the success of therapy. This is especially so when there is generalized vasoconstriction, as evidenced by an elevation of the systolic and diastolic blood pressures. The greatest danger during the acute phase of the generalized peripheral vascular constriction is the extra strain upon the heart. Butler and Reyersbach<sup>43</sup> state that "almost every case that dies in the acute stage of the disease dies of cardiac insufficiency."

**Magnesium sulfate** is the drug of choice for relief of this type of vascular spasm. The drug is injected intravenously and/or intramuscularly in an amount to attain a plasma magnesium level of 5 milliequivalents per liter (normal 1.5 milliequivalents per liter). A decrease in the hypertension is evidence of effective treatment. The advantages of complete *bed rest* seem unquestioned. A *salt-free liquid diet* and a limitation of total fluid intake are prescribed when edema is present. *Sedation* is often necessary and in such instances *phenobarbital* is probably the drug of choice. *Digitalis* should be administered when

there is evidence of cardiac decompensation.

Butler and Reyersbach report a case of glomerulonephritis with progressive kidney involvement in which surgery was employed in the hope of increasing renal function. Initially, decapsulation of the right kidney was performed, the only improvement being a slight increase in urinary output. Sixteen days later, a left-sided lumbodorsal sympathectomy and decapsulation of the left kidney were performed. Postoperatively, the blood pressure became greatly elevated and magnesium sulfate was given intravenously for its control.

After a stormy course, the boy was once again subjected to surgery in order to reduce the hypertension and to improve the renal function. A right lumbodorsal sympathectomy was performed three weeks after the left had been done. Following the second operation, there were decreased nonprotein nitrogen content of the blood, a decreased serum phosphorus, and an increased serum calcium. The child was in the hospital for four months. On examination five months after discharge, he had lost his edema and his blood pressure was normal; urine analysis still showed albumin, red



blood cells, white blood cells, and casts. The authors suggest that surgical therapy be considered where glomerulonephritis has been present for a considerable time and the elevated blood pressure is not lowered by magnesium sulfate therapy.

### Chronic Glomerulonephritis

**Treatment**—Bradley<sup>44</sup> discusses the therapy of chronic glomerulonephritis. Treatment of chronic glomerulonephritis is concerned with the replacement of protein, electrolytes, and fluids, when necessary, and in the eradication of or, more important, in the prevention of foci of infection. Alterations of the body chemistry result from the abnormal renal physiology. Laboratory procedures may be employed to determine the vascular status and to gauge the replacement therapy. The carbon dioxide combining power, the plasma chloride, calcium, inorganic phosphorus, protein levels, and urinalyses are required for adequate evaluation. It should be recognized that the injection of protein into the vascular system does not produce a corresponding rise of plasma protein because of the necessary replacement of cellular as well as of vascular protein; in other words, there is a vascular-extravascular protein equilibrium.

Diuresis may be necessary when edema and/or azotemia are present. Use of plasma may so alter the oncotic pressure that diuresis may take place from the extravascular fluid being drawn into the vascular bed. *Urea* and *mannitol* as well as *potassium* and *ammonium chloride* may be effective in increasing fluid output. *Mercurial diuretics*, in conjunction with previous ammonium chloride therapy, have been tried; however, mercury may have a nephrotoxic action. When there are a continued high specific gravity and azotemia, these drugs are contraindicated.

Patients in the nephrotic stage of chronic glomerulonephritis have an increasing susceptibility to infection, particularly with streptococcal and pneumococcal organisms. There is described a clinical syndrome known as the nephrotic crises. In this condition there is a sudden onset with fever, often with peritonitis, which may be sterile or bacterial in origin. Another feature is the hypoaaminoacidemia. Treatment includes intravenous *amino acids*, *sulfonamides*, and or *penicillin*, and transfusions of *whole blood*.

### Treatment of Renal Infections

There are now effective therapeutic agents for combating most urinary tract infections. The identification of the organism is of the utmost importance in the choice of medication. *Sulfonamides* and *mandelic acid* are almost interchangeable in treatment. However, the proteus bacillus is susceptible only to the sulfonamides while the Streptococcus foecalis usually responds to mandelic acid. Mandelic acid must be given in large dosage and with sufficient enteric-coated ammonium chloride tablets to render the urine more acid than a pH of 5.5. Penicillin is effective against gram-positive cocci but ineffective against gram-negative rods.

The criteria of cure, as reported by Campbell,<sup>45</sup> is at least two negative urine cultures and/or smears following a course of therapy for eight to ten days. Unless the urine is sterilized, the infection will recur. If therapy is not successful in an acute case within two to three weeks, or in a chronic case within four weeks, a complete urologic investigation should be undertaken. One danger of the present-day therapy is that the urine may be sterilized in spite of even an obstructive lesion which produces stasis in the urinary tract. Thus, repeated

attacks of so-called "pyelitis" should not be repeatedly treated with these drugs, but the underlying pathology should be investigated by urologic means. The author estimates that only in one third to one fourth of all cases does chemotherapy alone achieve full benefit for the patient. One must aim, above all, in the prevention of secondary changes in the upper urinary tract, *i. e.*, the preventing of renal damage.

### Extrarenal Uremia

The clinical syndrome of extrarenal uremia, discussed by Donovan and Murphy,<sup>46</sup> may be produced by a number of different factors. The underlying pathologic physiology results from a disturbance of the circulation producing alteration of renal function with azotemia. This condition occurs clinically in states of dehydration and shock. Physiologically, there are present an increased oncotic pressure, a diminution of blood flow, and a decreased blood pressure which results in a diminution of effective filtration pressure of the kidney. During this period, albumin and casts are found in the urine, and the blood nonprotein nitrogen is elevated. Urinary findings

disappear as glomerular function improves.

Extrarenal uremia is found in those disease states where dehydration is a feature, as in cases of excessive diarrhea, vomiting, insufficient water intake, and diabetic acidosis. The nitrogenous retention following intragastrointestinal hemorrhage is partially due to the digestion and absorption of blood protein. The aim of treatment is the restoration of blood volume and blood flow, correction of dehydration, replacement of blood, plasma, and/or electrolytes, and correction of acidosis or alkalosis when present.

### Protein Content of Edema Fluid

The protein content of edema fluid in patients with acute glomerulonephritis is the same as the protein content of edema fluid of cardiac origin (Warren and Stead<sup>47</sup>). Edema in acute nephritis is not the result of a diffuse capillary damage, but stems from a disturbance in renal function which results in water and salt retention. However, it should be realized that cardiac insufficiency may occur in acute nephritis. Nevertheless, altered renal function is the cause of edema rather than cardiac failure.

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## HEART DISEASE IN CHILDREN

ROBERT A. LYON, M.D.

### Diagnosis

The position of the various chambers and great vessels of the heart in roentgenograms as demonstrated by angiocardio-grams has been reviewed by Sussman and Grishman.<sup>48</sup> In anterior posterior views of the normal heart, the right border has been shown to consist only of the right auricle and ascending aorta. The left border consisted only of the left ventricle and the pulmonary artery. The

pulmonary conus did not show and the left auricular appendage did not form a portion of the left border in angiocardio-grams.

In the right oblique views, the pulmonary artery constituted the entire middle portion of the left cardiac border and only in lateral views did the pulmonary conus come into relief. In left oblique views, the right cardiac border in its most inferior region was made up

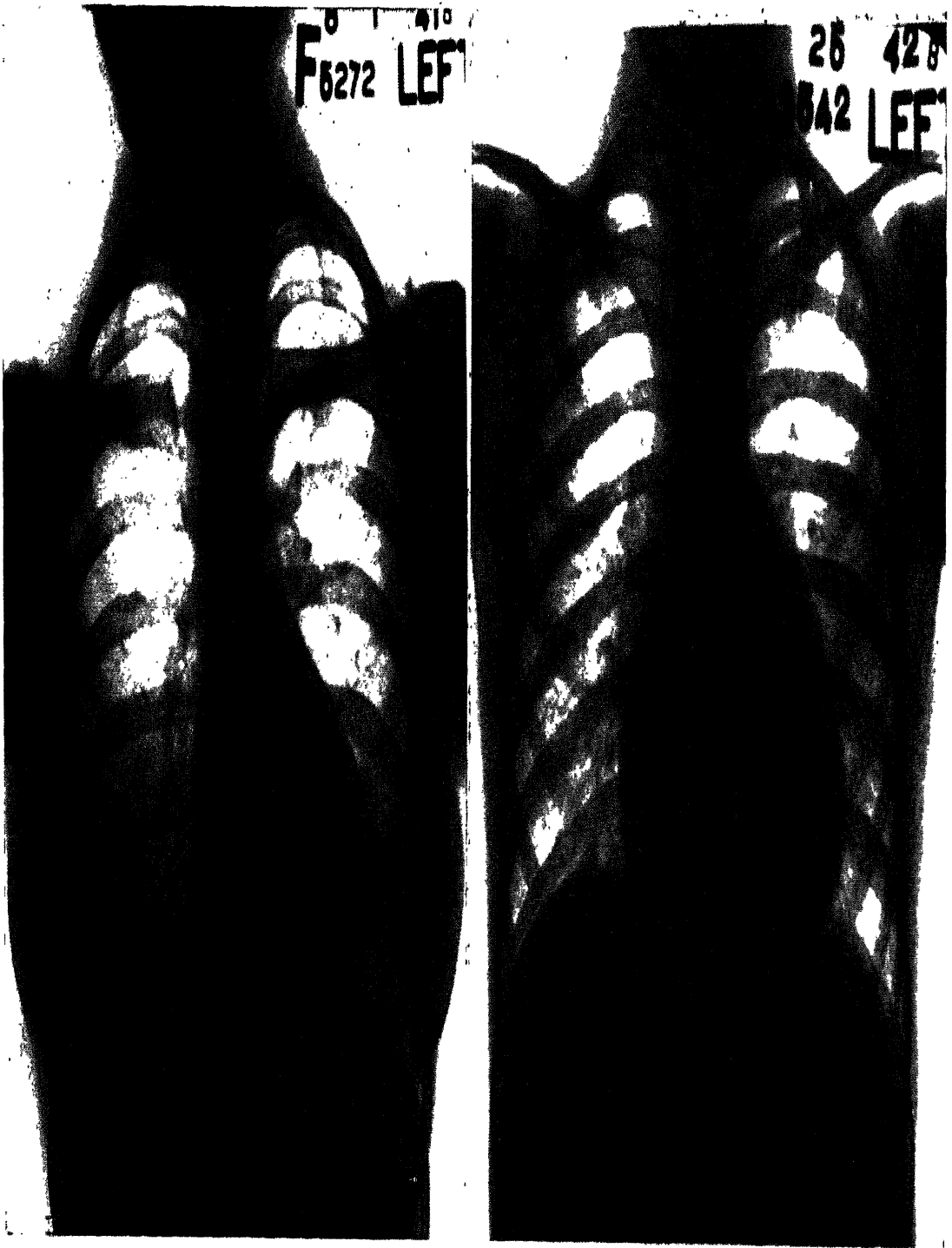


Fig. 1—Cases of isolated pulmonic stenosis. On the left, the pulmonary artery is small. On the right, there is a poststenotic dilatation of the pulmonary artery. The convex "middle left curve" is due mainly to dilatation of this vessel. (Sussman, M. I. and Grishman, A.: *Am. Heart J.* 28: 653 (Nov.) 1944.)

of the right ventricle but it might be obscured by the right auricle. The lower left border was composed of left ventricle.

Enlargement of the right caused an increase in the total width of the ventricular area and made the pulmonary artery more prominent on the left cardiac border. Enlargement of the left

of the gas bubble in the stomach. (See illustrations.)

### Congenital Heart Disease

A striking operation for the relief of patients with stenosis of the pulmonary artery has been devised by Blalock and Taussig.<sup>49</sup> An anastomosis of the sub-

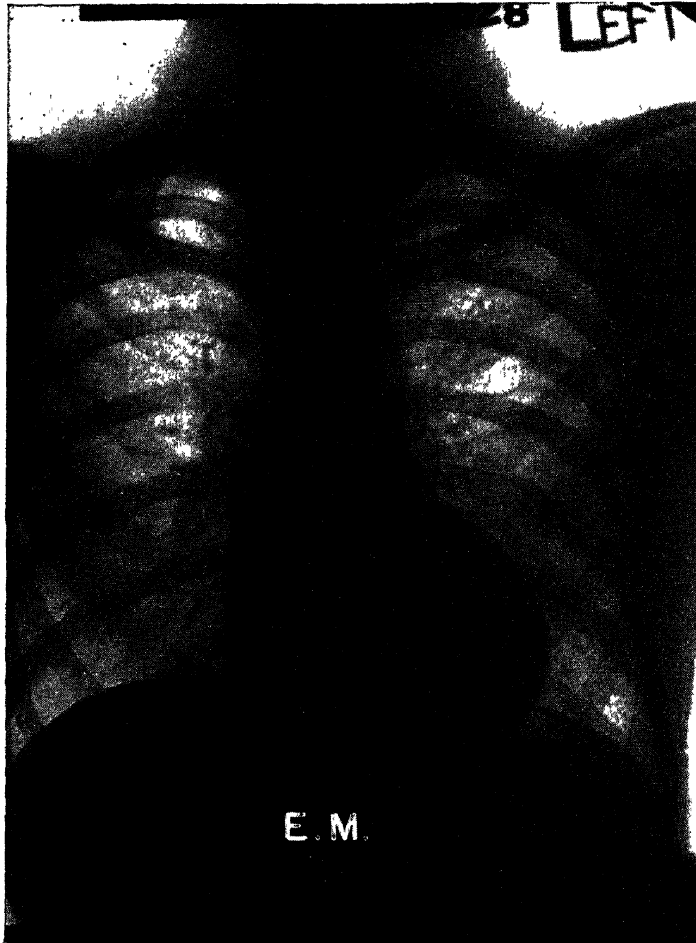


Fig. 2—Marked hypertension in a case of coarctation of the aorta. The patient was asymptomatic. (Sussman, M. L. and Grishman, A.: *Am. Heart J.* 28: 657 (Nov.) 1944.)

auricle caused a straightening or convexity of the left cardiac border. In the right lateral or oblique views, it displaced the esophagus posteriorly at the level extending from the branching of the left bronchus to the point at which it entered the diaphragm. An enlarged left ventricle extended downward to the left until its shadow merged with that

clavian or innominate artery with the pulmonary artery to increase the amount of blood flowing through the lungs led to marked improvement of three children with deep cyanosis and dyspnea due to the tetralogy of Fallot. The cyanosis grew less or disappeared and the patients were able to be much more active without dyspnea. The red cells and hemo-

globin decreased and the oxygen content of the arterial blood rose. The authors emphasized the fact that the operation could not be of value to all patients with cyanosis but only to those with impairment of circulation to the lungs. The patients who should receive benefit are those with pulmonary stenosis or atresia, and those with truncus arteriosus with bronchial branches. Patients with transposition of the great vessels and those with aortic atresia would not benefit from the operation. Important in the preliminary examination is the deter-

The diagnostic features of patent ductus arteriosus as it occurred in uncomplicated form in sixty-two patients has been reviewed by Shapiro.<sup>50</sup> Some of the patients have been observed for as long as ten to twenty years. The most common sign was the typical to-and-fro murmur which was present in every instance except one. In that patient no murmur at all was heard and the ductus at autopsy proved to be very large. A thrill was present in fifty-three instances and absent in nine. The blood pressure and pulse pressure were high in forty-

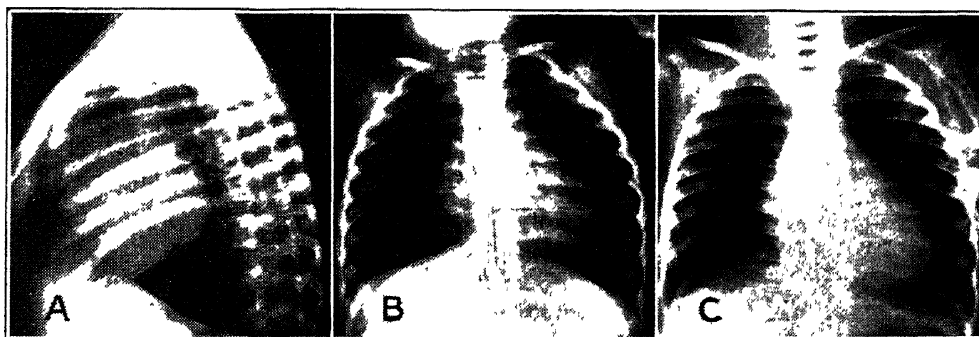


Fig. 3—(Case 1.) Appearance before and after operation: *A*, Left anterior oblique view before operation; *B*, anteroposterior view before operation; *C*, anteroposterior view after operation. (Blalock, A. and Taussig, H. B.: *J. A. M. A.* 128:189 (May 19) 1945.)

mination of the size of the pulmonary artery. In roentgenograms or fluoroscopy, the left side of the heart shows a concave border due to hypoplasia or absence of the pulmonary artery. In rare cases of complete transposition of vessels, a similar picture is obtained when the pulmonary artery lies behind the aorta. Fluoroscopic examination of the patient in the left oblique position will demonstrate the pulmonary window when the pulmonary artery is small.

The optimum age for operation seemed to be four to six years. In the patients reported, there was no evidence of severe impairment of circulation of the arm or brain after the subclavian or innominate arteries were severed.

eight patients and normal in fourteen. Thirty-three patients appeared normal in respect to their nutritional status, twenty-three were stunted in growth, and six were obese. In the great majority of instances, the electrocardiographic findings were normal. Five had slight degrees of left axis deviation, one had a right axis deviation, and other slight changes were noted in four. Roentgenologic examination showed slight enlargement in twenty-one, moderate enlargement in fifteen, and pronounced enlargement in four. In ten patients, the size of the heart was normal. The pulmonary artery was almost always enlarged and could be demonstrated most readily in oblique views. The pulmonary

branches in a few instances were notably enlarged. In the differential diagnosis, the author mentioned the venous hum which occurs occasionally at the base of the heart but changes in quality with movement of the child's head from side to side or by pressure with the finger on the neck vessels. The diastolic murmur and high pulse pressure of aortic regurgitation sometimes suggested a diagnosis of patent ductus arteriosus. In the case of interauricular or interventricular septal defects, there may be an enlargement of the pulmonary artery,

and Tannenbaum<sup>51</sup> observed an eighteen-year-old girl who had a severe illness with blood cultures positive for streptococcus viridans. Following the ligation of the ductus, the patient made a rapid recovery and has remained well for a two-year period of observation.

The possibility that congenital laryngeal stridor may be caused by persistent right aortic arch has been suggested by Faber, Hope, and Robinson<sup>52</sup> because of two such cases they had observed. In their review of the literature, they found that previous to 1938 there had been

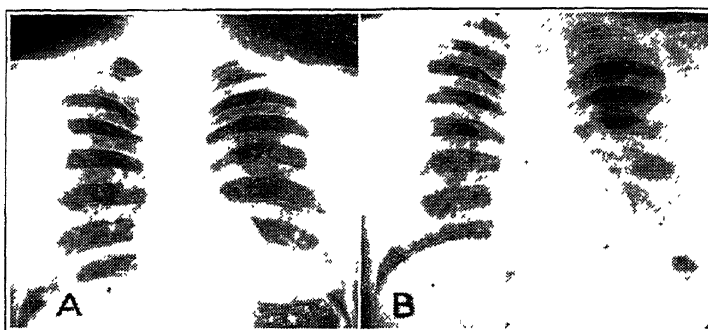


Fig. 4—(Case 2.) Heart, *A*, before operation, and *B*, one month after operation. (Blalock, A. and Taussig, H. B.: *J. A. M. A.* 128: 189 (May 19) 1945.)

and ventricular hypertrophy as in patients with ductus arteriosus patency, but the type of murmurs and blood pressure determinations generally made the differentiation easy. In summary, the diagnostic criteria of patent ductus arteriosus included the machinery murmur, the thrill in the pulmonic artery area, enlarged pulsating pulmonary vessels, an enlarged heart, increased pulse pressure, stunting of growth, the absence of cyanosis and clubbing, a normal electrocardiogram and a history of heart disease from early childhood. The importance of making an accurate diagnosis for the purpose of operation was emphasized.

The ligation of a patent ductus of a patient who apparently had a bacterial endocarditis led to a cure without the use of specific drug therapy. Bettman

113 reports of this malformation of the great vessel and in about 13 instances the diagnosis had been made during the lifetime of the patient. By 1943, nine cases had been reported in infants, and four had been diagnosed during their lifetime. The stridor is present most of the time in these patients and is more severe after crying and eating. It may be so severe that there is retraction of the tissues in the suprasternal notch and the epigastrium. Cyanosis has been noted in some instances, with a tendency for extreme extension of the head. The symptom is less marked during sleep, and is exaggerated, of course, during respiratory infections. The other common symptom is that of dysphagia because of compression of the esophagus. There are no typical physical findings

and no murmurs. The diagnosis is made by fluoroscopy or roentgenogram. When the patient ingests barium, his esophagus can be seen to be displaced to the left in anterior views. In the lateral or oblique views, the esophagus is pushed forward at the level of the great vessels. The right aortic knob lies to the right of the mediastinum and fluoroscopy or kymoroentgenograms demonstrate pulsation at this point. In rare instances there is a double aortic arch and in some cases the esophagus is constricted uniformly and is displaced forward.

administration of digitalis, the heart rate dropped to 114 and the child's condition improved. No further attacks have been observed during a period of one year of observation. A series of eight other infants less than two weeks of age has been reported in the literature, and in one instance the disease was suspected before the birth of the infant. In previous reviews, nineteen patients under a year of age had been reported, and of the sixteen treated with *digitalis* fifteen recovered. The one patient who died had a complicating sarcoma of the conduction

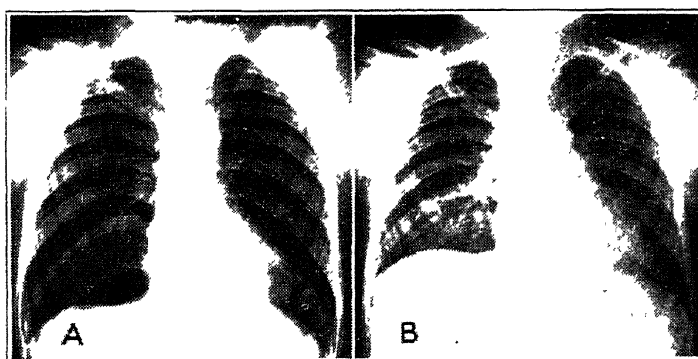


Fig. 5—(Case 3.) Heart, *A*, before operation, and *B*, two weeks after operation. (Blalock, A. and Taussig, H. B.: J. A. M. A. 128: 189 (May 19) 1945.)

Three infants with congenital heart disease, whose mothers had rubella in the second month of pregnancy, were described by Swan.<sup>53</sup> Two were born prematurely, one had a patent interventricular septum, and all had a widely patent ductus arteriosus and various stages of patency of the foramen ovale. Two also had congenital cataracts and all died within ten months after birth. (See also Diseases of the Newborn.)

### Arrhythmia

The occurrence of paroxysmal tachycardia in an infant four days of age has been reported by Howard.<sup>54</sup> The pulse rate was 300 per minute and the child had symptoms of cyanosis and dyspnea. Within eight hours after the

system. All of the patients in this age group have either auricular or nodal tachycardia. Ventricular tachycardia has not been observed.

### Hypertension

Malignant hypertension may occasionally be caused by a unilateral kidney lesion. In a report by Kennedy, Baker, and Walters,<sup>55</sup> an atrophic kidney associated with chronic pyelonephritis and malignant hypertension occurred in a child seven years of age. The removal of this kidney was immediately followed by a reduction of blood pressure to normal levels. When the patient was observed five years later, the blood pressure was still normal and the authors believed that the cure was a permanent

one and that the prognosis was good. In some previously reported cases, only temporary improvement followed nephrectomy but whenever the pathological process was fairly recent so that the changes had not become extensive and irreversible, the prognosis following operative procedures was much better.

### Subacute Bacterial Endocarditis

Among 250 patients with subacute bacterial endocarditis reviewed by Kelson and White,<sup>56</sup> there were about 50 who were less than twenty years of age. The youngest occurred in a patient two and one-half years old. The most frequent signs of the condition were the presence of cardiac murmurs denoting the existence of heart disease; the presence of petechiae which occurred in 87 per cent of cases; an enlarged spleen (59 per cent) and less frequently hematuria, clubbing of the fingers, and chills. The disease was frequently not suspected during the early stages and was most commonly confused with grippe, although rheumatic fever, meningitis, pneumonia, tuberculosis, or intracranial lesions were also diagnosed at the onset of the condition. Very frequently the bacterial endocarditis was preceded by respiratory infections and quite frequently it followed the extraction of teeth. Rheumatic heart disease was present in 90 per cent of cases and congenital defects in 5 per cent. The most frequent congenital defects were patency of the ductus arteriosus and defects of the interventricular septum. All of these patients had been observed prior to 1940 and death occurred in every instance. The majority survived three or four months after the diagnosis was made, but eighteen lived more than one year and one patient lived as long as nineteen months. Various types of treatment were tried in these patients but none gave favorable

results. *Sulfanilamide* and *sulfapyridine* had been employed in some of the recently observed patients of this group and, although this therapy had caused a reduction in fever and negative blood cultures for a short period of time, none of the patients survived.

In a review of bacterial endocarditis occurring in 197 patients, Kelson<sup>57</sup> found that sulfapyridine had been the most effective drug in reducing temperature and making the blood stream sterile. Only four of the total group, however, could be considered to be cured. Such complications as the cerebral embolism, congestive failure, and the toxic reactions to the drug were also included in the causes of death. *Heparin* was used in a number of patients and seemed to be effective in reducing the incidence of cerebral embolism but was ineffective unless a sulfonamide or penicillin was administered at the same time. *Penicillin*, used in a small number of patients for a short period of time, seemed to be less toxic and probably was less apt to produce a resistant strain of bacteria.

The results of treatment of ninety-two patients with bacterial endocarditis with sulfonamides and penicillin have been reviewed by White, Mathews, and Evans.<sup>58</sup> Six or possibly seven of these patients had apparently recovered. Among the sulfonamides, sulfapyridine had produced the greatest antipyretic effect. With the other drugs, the fever disappeared for as long as two to twelve days but then recurred. Seventeen patients received heparin along with the other treatment and, of those who recovered, three had received the drug and two had not. *Dicoumarin* has also been used as an anticoagulant in association with the other treatment with no discernible effect on the prognosis. Since January, 1944, nine other patients with subacute bacterial endocarditis have received large



doses of penicillin. Two of this group have died; one of embolism of the brain and the other of acute rheumatic fever. The remaining number of patients seem to be greatly improved although there have been only a few months of observation of this group. There was no evidence that early treatment of the disease led to recovery any more rapidly than did treatment started in the later stages of the infection.

A series of twenty-seven patients with subacute bacterial endocarditis was treated with penicillin by Dawson and Hunter.<sup>59</sup> Of the group, fourteen recovered and remained well for a period of three to twenty-two months. Seven had been well for a shorter period of time. Three have had relapses since the treatment was discontinued and three died of cerebral embolism. The daily dosage of the drug varied from 80,000 units to 500,000 units and the total amount per patient ranged from 830,000 to 36,700,000 units. In the most recently treated patients, the continuous intramuscular drip method was employed with good response on the part of the patients. The blood levels were higher than those obtained by intravenous drip. Heparin was used as an adjunct to the therapy in the majority of instances. When the streptococci obtained from the blood stream were tested for their resistance to penicillin, there was considerable variation of resistance but the clinical course of the patients did not parallel these characteristics of the infecting organism.

**Heart Disease**—A child with subacute bacterial endocarditis observed by Collins<sup>60</sup> responded well to penicillin therapy. The patient developed endocarditis shortly after recovery from a severe respiratory infection and blood cultures were repeatedly positive for streptococcus viridans. The patient showed no

response to *sulfamerazine* but treatment with penicillin resulted in rapid improvement. The therapy, which was instituted two months after the onset of the bacterial endocarditis, consisted of daily doses of 100,000 units until a total of 1,400,000 units had been given over a two-week period. The child's temperature fell to normal on the second day after the treatment was started and blood cultures soon became negative. The patient remained symptom-free for six months, at which time the report was made.

### Rheumatic Fever

**Incidence**—The importance of rheumatic fever as a cause of heart disease and death in children and young adolescents has been emphasized by Wheatley.<sup>61</sup> As may be seen from the accompanying charts (Charts I, II, III) rheumatic fever was the leading cause of death in children five to fourteen years of age. It surpassed appendicitis, pneumonia, communicable diseases, tuberculosis, and other conditions. Among the first two million draftees examined by the Selective Service System, approximately 2 per cent were unqualified because of rheumatic heart disease. The author emphasized the need for the more universal application of standards for diagnosis and care for these patients, the need for further studies of the disease, and for educational programs for professional and lay groups.

The incidence of rheumatic fever among California children, which has been determined recently by Sampson, Hahman, Halverson, and Shearer,<sup>62</sup> showed considerable variation in respect to the climate of the three areas investigated. In a warm, dry region, the incidence was relatively low, similar to that reported in San Francisco or Cincinnati. In a mountain region where wider ex-

tremes of warm and cold weather occurred, the incidence was higher, resembling the rates in New England or Great Britain. An unusually high incidence of rheumatic fever and valvular disease was discovered in an area with a uniformly cool climate and heavy rainfall. In addition to climate, certain factors such as age, sex, race, and housing conditions seemed to have some

instance. Among the patients with respiratory infections and scarlet fever, the most frequent types discovered were 19, 17, 30, 3, 1, 36, and 6, and among rheumatic fever patients the types were closely parallel. In the case of the rheumatic fever patients, however, the cultures were frequently made during the acute attacks of the disease and were not obtained during the initial respira-

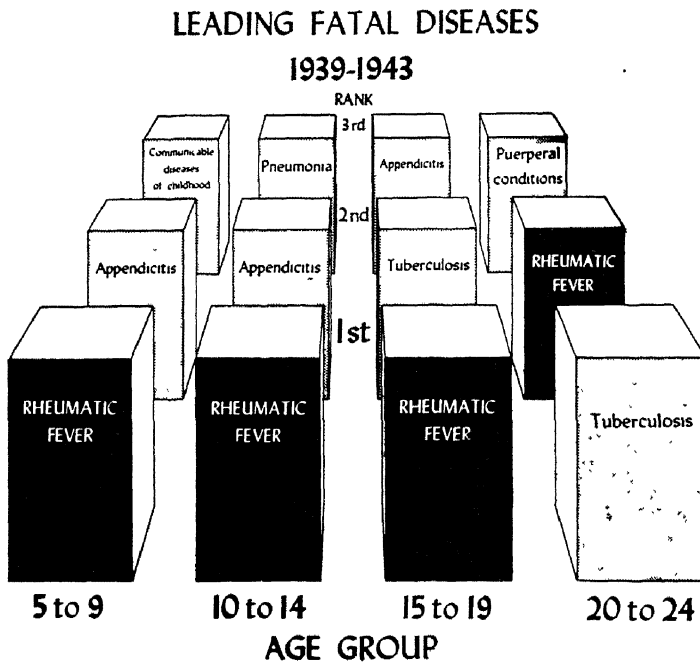


Chart I—Rheumatic fever ranks high as a cause of death in young people (Metropolitan Life Insurance Company). (Wheatley, G. M.: J. Pediat. 26: 237 (March) 1945.)

slight bearing on the incidence of the disease.

**Heart Disease**—A survey of the geographic distribution of hemolytic streptococci in eight Army posts of the Air Forces in various parts of the country has been made by Van Ravenswaay.<sup>68</sup> The number of cultures obtained varied from 245 to 3222 in the individual posts. The incidence of the hemolytic streptococci was much greater in the troops situated in the Rocky Mountain area than in southern parts of the country. The streptococci were typed in every

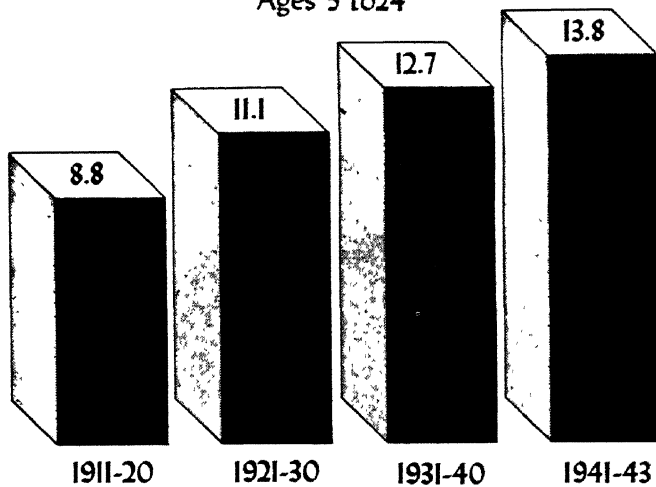
tory infections. When serial examinations of the throat flora of the rheumatic fever patients were made, the cultures often changed to different types of streptococci as time went on. Among the patients located in the camps of the South, there was less tendency for the type to change and the one type persisted for a considerable length of time. With the prevalence of streptococcal infections in the patients of the southern camps, it seemed strange that rheumatic fever did not occur more often. Instead, the incidence rates of both scarlet fever

and rheumatic fever were considerably lower than in the northern areas.

In a study of the incidence of recurrences of rheumatic fever, Wilson and Lubschez<sup>64</sup> emphasize the importance of the age of the patient and the interval since his last attack. Among patients four to thirteen years of age, recurrences were noted in 25 per cent, although the

per cent after three years. Within the year immediately following a rheumatic fever infection, 38.7 per cent of patients developed recurrences. Patients who had had several attacks of the disease did not suffer recurrences more frequently than those who had had a single attack. The severity of the disease and the presence of active carditis likewise had no

**DEATHS FROM RHEUMATIC FEVER  
AND HEART DISEASE  
As Percent of All Fatal Diseases  
Ages 5 to 24**



Metropolitan Life Insurance Company, White Industrial Policyholders

Chart II—Rheumatic fever causes an increasing proportion of the total mortality among the children (Metropolitan Life Insurance Company). (Wheatley, G. M.: *J. Pediat.* 26: 237 (March) 1945.)

rates varied with the age of the patient. Of the children fourteen to sixteen years of age, 8.6 per cent had recurrences and among the group of patients older than sixteen years, the rate was 3.7 per cent. It was much more common for recurrences to occur within the year after an attack than after longer intervals had intervened. The incidence of recurrences was 20.6 per cent when one year intervened after an attack, 10.7 per cent after two years following an attack and 6.6

influence on the recurrence rate. The living conditions and other environmental factors surrounding the child seemed to have no influence on the recurrence rate. The authors called attention to the importance of considering these various conditions that influence recurrence rates when studies are made of methods to prevent recurrences.

*Etiology*—Further pathological evidence of similarity between the lesions of rheumatic fever and those produced

in experimental animals by anaphylactic hypersensitivity has been reported by Rich and Gregory.<sup>65</sup> Sterile horse serum, powdered egg albumin, and the toxin of hemolytic streptococci have been injected intravenously to produce hypersensitivity in rabbits. Typical Aschoff bodies in the myocardium and in perivascular areas were produced.

was 7.5 members, which is higher than the general average of middle class families and makes necessary the consideration of economic factors, accounting for the scanty use of the more costly foods high in protein and vitamins. The low incidence of rheumatic fever among Eskimos and other groups of persons living on diets of fish or other animal foods and

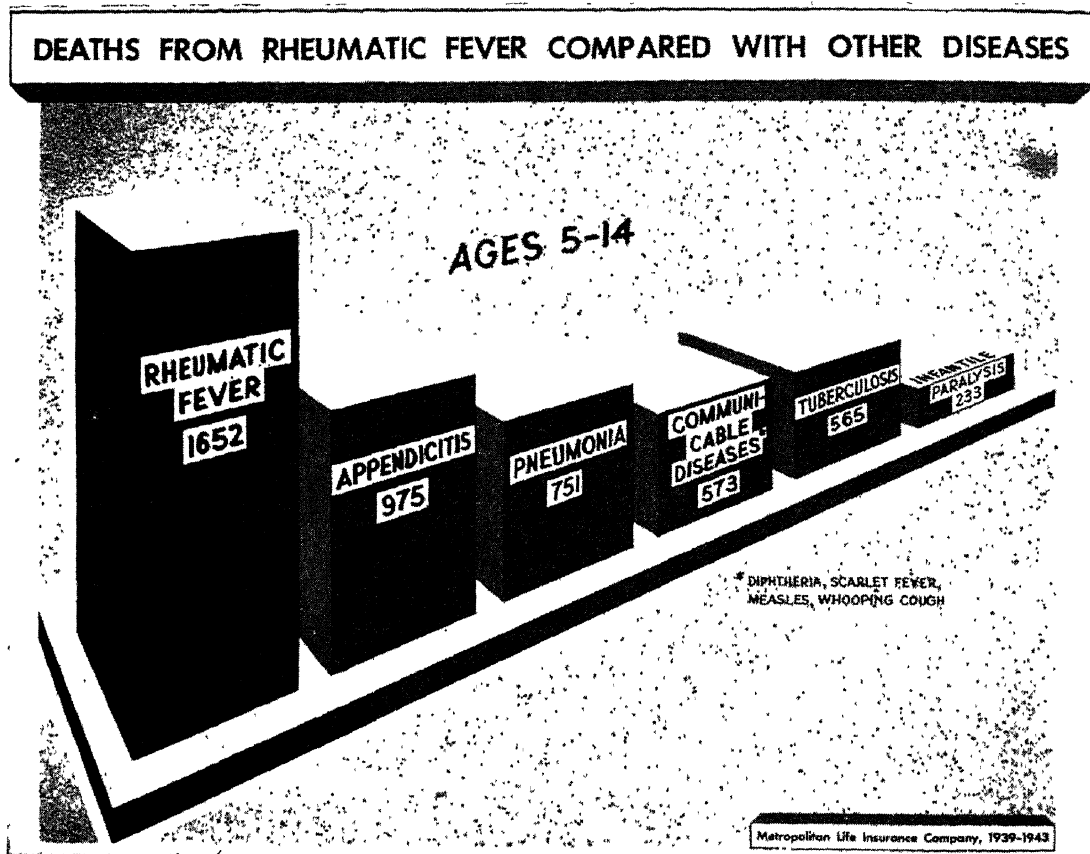


Chart III.  
(Wheatley, G. M.: J. Pediat. 26:237 (March) 1945.)  
(Metropolitan Life Insurance Company.)

The average diet of fifty rheumatic patients, as surveyed by Peete,<sup>66</sup> was found to be deficient in foods supplying vitamins A and D, calcium, phosphorus, and iron. In comparison with the food intake of normal children, the rheumatic patients also had some deficiency in proteins and an excess of starches and sugars. The average size of the rheumatic family

a low incidence of the disease among the upper classes, who are able to find well-balanced diets, indicate that nutritional factors have an important part in the etiology of rheumatic fever.

*Diagnosis*—The criteria for the diagnosis of rheumatic fever have been reviewed by Jones.<sup>67</sup> The demand for accurate diagnostic methods has been

stimulated by the development of community programs for the detection and the prevention of the disease. Among the major manifestations are carditis, migratory joint pains, chorea, subcutaneous nodules, and the tendency for recurrences of rheumatic fever. A combination of these signs makes the diagnosis reasonably certain. Carditis is not always easy to diagnose but the presence of a blowing systolic murmur at the apex, or possibly a diastolic murmur at the base, together with cardiac enlargement, is usually indicative of cardiac disease. There may be some changes in the electrocardiogram such as prolongation of the auriculoventricular conduction time or the inversion of the T-waves. The sleeping pulse rate is often faster than normal. Arthritic joint pains of a migratory nature are common, although they are not always rheumatic in etiology, but when there has been a preceding respiratory infection and other evidence of rheumatic fever, they are of great diagnostic importance. Chorea seems to be closely related to rheumatic fever. In the author's experience, about half of all rheumatic fever patients have chorea at some time, while three fourths of the chorea patients generally develop other manifestations of rheumatic fever. Subcutaneous nodules rarely precede the other evidence of carditis and rheumatic fever but, when present, are of diagnostic value, especially of the activity of the disease. Recurrences of rheumatic fever are important. In the author's experience, 70 per cent of young rheumatic fever patients had recurrences within ten years after the initial attack. Minor manifestations of rheumatic fever include such symptoms as fever, abdominal pain, precordial pain, skin rashes consisting most frequently of erythema marginatum and occasionally purpuric manifestations, epistaxis, and pulmonary involvement.

Certain laboratory findings of importance are microcytic anemia, leukocytosis, and an elevation of the sedimentation rate, although the latter test is occasionally normal in the presence of heart failure. Less frequent minor manifestations include fatigue, pallor, sweating, loss of weight, headache, vomiting, and hematuria. Many of these manifestations may occur with other diseases, but when two or more occur together they are often indicative of a rheumatic infection.

In the differential diagnosis, the diseases most commonly considered are poliomyelitis, osteomyelitis, other skin diseases, and nephritis. Less frequently Still's disease, rheumatoid arthritis, and disseminated lupus erythematosus present problems of differential diagnosis. The differentiation of appendicitis and the abdominal pain of rheumatic fever may offer difficulty. Two other factors which may aid in recognizing rheumatic fever are its presence in other members of the family and its response to *salicylate therapy*.

Skin reactions to injections of specific protein antigens or "M" fractions of streptococci were found to be positive more frequently in rheumatic children than in normal groups, according to Taran, Jablon, and Weyr.<sup>68</sup> The specific proteins of twenty-five different types of hemolytic streptococci were grouped into five solutions, each containing the antigens of five strains. Cutaneous reactions occurred in 65 per cent of normal children and in 85 per cent of the rheumatic patients. The reactions were also more severe in the latter group, but the age of the patient and the stage of activity of the rheumatic process had no influence on the incidence rate or degree of reaction. The normal siblings of rheumatic patients had as frequent

and as severe reactions as the rheumatic patients.

**Complications** — Peritonitis preceding rheumatic fever infection has been observed in three children and one adult by Berger.<sup>69</sup> Three general types of abdominal complications of rheumatic fever have been described. First is a digestive upset; second, the symptoms suggestive of appendicitis; and third, those simulating peritonitis. Any type may occur before rheumatic fever is diagnosed or it may develop later in the course of the disease. Occasionally these symptoms have been the only manifestations of rheumatic fever. In the patients reported by the author, the abdominal symptoms responded to the administration of salicylates and *sodium bicarbonate* and did not respond to the administration of *sulfonamides*. In none of the instances did the rheumatic fever precede the occurrence of the abdominal symptoms, although in one case there was a family history of the disease. The adult patient may also have had subacute bacterial endocarditis, but she did not respond to sulfonamide therapy and improved immediately after the administration of salicylates. Subsequently, however, she developed a blood stream infection with *Streptococcus viridans* and in spite of treatment died. When such vague symptoms of abdominal pain, nausea, and vomiting occur without the presence of definite masses or areas of tenderness in the region of MacBurney's point, a trial course of salicylates is justified.

**Treatment** — Intensive *salicylate therapy*, which has been recommended by Coburn for the treatment of acute rheumatic fever, has been tried by Wégria and Smull.<sup>70</sup> A group of seventeen patients who had suffered a total of nineteen attacks of acute rheumatic fever received the treatment. So-

dium salicylate was administered intravenously or by mouth as enteric-coated tablets containing 0.3 gm. each. The dosage was adjusted so that the patients developed blood levels of 350 to 500 gamma of salicylate, which seemed to be the optimum therapeutic level, without producing symptoms of salicylate poisoning. Another group of nineteen patients who had short courses of therapy or none at all were observed as a control series. The sedimentation rate was employed as a measure of the effectiveness of the drug. High sedimentation rates continued for about two weeks and had fallen nearly to normal levels by the sixth week in about the same number of patients of each group. In one or two patients, the response seemed to be good. The course of the disease did not seem to be shortened by the salicylate therapy, although the authors wondered whether early institution of the treatment within a few days after the onset of the rheumatic fever might not have been more effective.

The danger of salicylate poisoning has been pointed out by Hartman.<sup>71</sup> In his experience, about 50 per cent of the patients who had serious clinical signs of salicylate poisoning died. The drug seems to exert its primary antipyretic and analgesic effect upon the hypothalamus and optic thalami of the brain. Respiration is stimulated at first but the initial periods of restlessness and excitement are followed by stupor, coma, and hemorrhages in various organs. A depletion of liver glycogen, vitamin C, and a delay of coagulability of the blood have been reported by various authors. The hyperventilation which is produced initially leads to a reduction of the plasma  $\text{CO}_2$ , and occasionally an elevation of the pH but more frequently, in the author's experience, an acidosis developed. The best treatment seemed to be

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meningitis, and pneumococcic infections. The use of any one of the sulfonamides in doses of approximately 1 gm. a day seemed adequate in carrying out this preventive program. One half a gram a day for young adults was only slightly less effective. In the case of rheumatic fever, it is necessary for the patient to be entirely free from the acute manifestations of the disease before the drug is started. Generally, the sedimentation rate should have reached normal and the symptoms of the active infection should have disappeared. Reactions to the daily administration of the drug have been very slight, consisting primarily of agranulocytosis and exfoliative dermatitis. It seemed to the author that when such prophylactic treatment was started, it should be continued daily for a period of at least five years and possibly longer if there seemed to be dangers of recurrences. Some of the patients so treated have likewise been conspicuously free from other infections such as erysipelas, otitis media, and other diseases. It is very important that the patient be watched carefully throughout such a prophylactic program to be sure that he is in good physical condition and is receiving an adequate diet. At the earliest sign of toxic symptoms, the dosage can be reduced or removed entirely for a short time and then the treatment can generally be instituted again without danger. Symptoms of rash and sore throat suggest toxic reactions and leukocyte counts must be made frequently to detect any evidence of leukopenia. Two other methods of prevention of rheumatic fever have been attempted. The injection of a filtrate of the hemolytic streptococcus has been claimed to reduce the incidences of recurrences. The daily administration of *salicylates* prophylactically has also been tried in some patients for periods of one month or longer

and this treatment also has seemed to offer some degree of protection against rheumatic occurrences.

The program for the control of rheumatic fever in the Army Air Forces has been reviewed by Holbrook.<sup>77</sup> Sulfadiazine administered in doses of 4 gm. during a forty-eight-hour period caused a definite reduction in the number of hospital admissions of patients with respiratory diseases. Smaller doses of 1 gm. a day were effective in reducing the number of hospital admissions and of dispensary visits, and even 0.5 gm. a day seemed to have a similar beneficial effect. Streptococcal infections especially seemed to be held in check by the daily administration of the sulfadiazine and it seemed probable that rheumatic fever would likewise occur less frequently. A 50 to 75 per cent reduction in the incidence of respiratory diseases and streptococcal infections was noted in the group treated with sulfadiazine as compared with that of the control series. Among a total of 40,000 troops who received the prophylactic treatment, 13 lost some days of duty, and 33 others had mild manifestations of infection not resulting in any loss of time. There were no complications involving the kidney or white blood cells. The most frequent reaction was a skin eruption occurring between the first to sixteenth day after the beginning of the treatment. Two individuals had high fever for a short period of time and one patient developed an anemia which was hemolytic in type. A total of 0.12 per cent of the group had mild reactions.

The experience of the Navy with a similar type of program has been outlined by Coburn.<sup>78</sup> The administration of 1 gm. of *sulfadiazine* daily was followed by a rapid decrease in the incidence of scarlet fever and respiratory infections. In various camps the drug



was given to unselected groups of sailors and the incidence of streptococcal infections among them was compared to that of a control series in the same camp. Among 30,000 treated patients, the treatment seemed to check the occurrence of respiratory infections, scarlet fever, and seemed to protect at least 85 per cent of the new arrivals who entered such areas, a record much better than that achieved in the control groups. The administration of 0.5 gm. of sulfadiazine produced an average blood level of 1.4 mg. per cent. It was assumed that about half this concentration of the drug would be present in the secretions of the respiratory tract. Mild reactions occurred in from 0.2 to 0.7 per cent of the patients treated, generally in the second or third week after the beginning of the treatment. The complications disappeared rapidly when the drug was withdrawn. When the drug was administered again, there was no evidence of sensitivity or an increase in the incidence of drug reactions. A few patients developed severe reactions consisting of exfoliative dermatitis and granulocytopenia. All but one of these patients recovered with symptomatic treatment. The one who died received large therapeutic doses of sulfadiazine while he was suffering from a drug rash and bronchitis, and autopsy showed evidence of leukemia. No strains of bacteria seemed to become resistant to sulfadiazine during this program of prophylaxis. This was indicated by the fact that there was no increase in the prevalence of any specific type of streptococcus nor in the number of streptococcal infections. All patients responded well to therapeutic doses of the drug when they developed acute infections after receiving the drug routinely.

The prevention of recurrences of rheumatic fever in children by the administration of sulfonamides has been reviewed

by Kuttner.<sup>79</sup> She had administered sulfanilamide during the winter months to a group of fifty-four children with rheumatic carditis and had selected another group of fifty-four children of similar age and sex to serve as a control series. Throughout two winters of observation, only one patient of the treated group developed a mild rheumatic attack following an infection with a group A streptococcus (type 6), while in the control group thirty of the fifty-four children developed streptococcal infections the first year and within a short time afterward had recurrences of rheumatic fever. In the second year, eighteen of fifty children in the control group developed streptococcal infections and all subsequently suffered rheumatic attacks. There were no signs of hypersensitivity to the sulfanilamide when the drug was again administered routinely four or five months after the previous course of treatment. It seemed probable to the author that sulfadiazine would be the most favorable drug to use because adequate blood levels can be maintained with small daily doses and reactions to this drug are generally mild. There has been no evidence that sulfanilamide may sensitize an individual to later therapeutic doses nor has there been any indication that sulfa-resistant strains of streptococci have been produced. When the drug has been withdrawn from patients treated for several years they are not usually susceptible to infections. The question remains whether long periods of administration of sulfa drugs interfere with the normal growth and development of the child. In the series reported by the author, weight gain of the patients was approximately the same in the treated as in the control series. It was her opinion that the drug should be started in young patients with first attacks and also in those who have val-

vular damage, and it should be continued for a period of five years or more to prevent the development of serious carditis.

The rôle of the cardiac clinic in the program for the care of the rheumatic patient has been reviewed by Rutstein.<sup>80</sup> The cardiac clinic should assume the responsibility of providing a diagnostic service to aid all of the physicians of a community, and it should provide for the necessary follow-up care of certain types of patients. It also may serve as a mechanism for the detection of patients with rheumatic fever who have not been under the care of a physician. Reporting of rheumatic fever to the public health departments is an important part of the program for the determination of the incidence of the disease but the diagnosis is difficult to confirm and physicians and hospitals have been lax in listing their cases. The clinic can be of service in examining siblings of patients with rheumatic fever and it should also serve as an educational center for the instruction of nurses and physicians regarding the general aspects of diagnosis and care of the rheumatic patient. To function adequately, the clinic should have a close connection with the hospital wards and be able to carry out all of the tests with the fluoroscope, electrocardiograph, and certain blood analyses which are necessary for arriving at the proper diagnosis. Nursing and social service help is essential for dealing with the individual problems which arise among the patients.

The methods by which rheumatic fever programs have been developed have been outlined in a series of reports by Hiss, Huse, Dwan, and Galvin.<sup>81</sup> Emphasis in most of these state programs or rural county programs has been placed on the provision of facilities for case finding, for diagnosis, and for the care of the rheumatic child. The programs are usually designed primarily for rural areas where there had previously been few specific facilities for diagnosis and care. In some instances, schools have played an important rôle in assisting with the detection of patients needing examination for an accurate diagnosis of heart disease. The schools have also cooperated in making necessary adjustments of programs for those who need some restricted activity, special occupational therapy, and vocational training. Cardiac clinics have been established in many areas to provide facilities for diagnosis and observation of the rheumatic fever patient. Educational programs for doctors, nurses, and for the laity have been developed to inform them of the newer concepts of rheumatic fever and the necessary care required for such patients.

Institutional care of the rheumatic child is also being provided more widely, in acute disease hospitals in some instances, or in convalescent or foster homes. Special schools are often advisable for the child with a mild form of disease. Here he may be kept under close medical observation while he proceeds with his school work in association with other children.

## MEASLES

RICHARD E. WOLF, M.D.

Bloxson<sup>82</sup> calls attention to a new method of protection against measles using *convalescent serum* obtained from an adult three days after the temperature was normal but while the rash was still present. This serum was given in daily doses of 0.4 cc. intradermally daily for five days, a total of 2 cc. The results obtained in forty individuals, thirty-eight of whom were children, indicates a high degree of immunity produced in this manner. There were only four cases of measles in the exposed group of forty treated by this method.

The author considers that the immunity produced may well be an active immunity since the dose is so small and the protection so great. He feels that when serum is obtained within a week after cessation of fever and rash, there occurs sufficient attenuated virus acting as an antigen to produce a potent active immunity when this serum is given intradermally. Proof of this hypothesis awaits the time when these same children have been exposed to succeeding epidemics.

Greenberg, Frant, and Rutstein<sup>83</sup> collected data on 814 measles contacts (between the ages of six months through six years) injected with 2 cc. of gamma globulin. Of the 814 patients, 78.1 per cent did not develop measles, 19.7 per cent developed mild measles, and 1.6 per cent developed moderate measles. None developed severe measles. In contrast, among ninety contacts receiving 5 cc. of placental globulin, 38.9 per cent did not develop measles, 37.7 per cent developed modified measles, and 23.3 per cent developed severe measles.

Among the 814 contacts injected with gamma globulin, reactions occurred in 7

or less than 1 per cent of the group. Two of the reactions were general, consisting of fever. The 5 local reactions consisted of slight induration at the site of the injection, lasting a few hours.

Among the ninety contacts injected with placental globulin, reactions occurred in thirty-seven or 41 per cent. There were eighteen general reactions, some of which showed anorexia, restlessness, as well as fever. Local reactions occurred in twenty-three and consisted of pain, swelling, redness, and induration at the site of injection lasting from one to two days.

The immunologic tests performed showed that the gamma globulin had a higher potency than the *placental globulin* and that therefore *gamma globulin* is the material of choice in the prophylaxis of measles.

Erickson<sup>84</sup> reviews the embryology of the fetal heart and eyes, and points out that important developmental changes are taking place in the eyes and heart early in fetal life. Since it is well known that embryonic tissues are peculiarly susceptible to virus infections, it is not difficult to understand the congenital malformations caused by rubella occurring early in pregnancy.

The author reports eleven babies born of mothers who were in the first two months of pregnancy when rubella occurred. All eleven of these babies exhibited congenital eye defects, usually bilateral cataracts. Nine of eleven had congenital heart defects.

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MUMPS

Siegel and Camp<sup>85</sup> report an unusual outbreak of mumps in an institution. Their data reveal the extent to which

uncontrolled conditions may vary. The incidence of the disease in the cottage in which the original mumps patient resided was significantly lower than in other cottages where there had been casual exposure only for twenty-four hours preceding clinical symptoms. In other words, there were fewer secondary cases among the group continuously exposed to the patient throughout his period of clinical mumps than there were

in the group exposed during the last twenty-four hours immediately preceding the clinical symptoms.

Had any means of prophylaxis been employed, it would have appeared highly efficient in the prevention of spread among exposed individuals. However, no prophylaxis being used, this experience illustrates how a single trial of a prophylactic measure may be erroneously interpreted.

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## NEWBORN

ROBERT A. LYON, M.D.

**Behavior**—The amount of crying of newly born infants which took place within a twenty-four-hour period has been observed by Aldrich, Sung, and Knop.<sup>86</sup> In the nursery, the infants tended to be most quiet and apparently satisfied during the morning hours when the greatest amount of attention was given to them. During certain hours late in the afternoon and at night, crying reached its greatest frequency. There seemed to be no indication that the crying of one infant stimulated the crying of another in this age group, but it seemed more probable that individual discomfort was the general cause. It was concluded that an important factor in satisfying the newborn infant was the distribution of nursing care fairly equally throughout the twenty-four-hour period so that the needs of the infant could be satisfied.

*Congenital malformations* occur in the offspring of animals when the mother has been fed a deficient diet during pregnancy, according to the studies of Warkany,<sup>87</sup> which have been reported recently. Mother rats, fed diets deficient in vitamin A and carotene, gave birth to offspring which, if they were able to

survive at all, were blind and had defects of the eyelids, the cornea, and other portions of the eye. The anterior chamber was frequently absent and the iris and ciliary bodies were malformed. Embryonic tissue replaced the normal vitreous substance and there was often a coloboma of the retina. Rats which were fed diets deficient in riboflavin usually produced young with abnormal skeletal structures, such as shortness of the mandible, radius, ulna, tibia, fibula, fusions of the ribs, cleft palate, and syndactylism of the fingers and toes. Maternal diets deficient in vitamin D frequently caused fetal deformities, such as curved long bones of the arms, legs, and ribs. Since there is a specific time in the gestation period when the various organs are formed, the deprivation of nutritional factors at these stages had its greatest effect. The author stresses the point, however, that his experiments have been limited to animals and the influence of nutritional deficiency in the human mother is not yet clearly defined.

Further evidence of the prenatal influence of rubella on the causation of congenital malformations of the newborn has been gathered by Erickson.<sup>88</sup> He

has observed eleven mothers who developed rubella in the second to fourth weeks of pregnancy and in every case the infant had some defect of the eye, such as bilateral cataracts, which occurred in the majority of instances, or micro-ophthalmia or corneal opacities, which occurred in four infants. Nine of the infants also had congenital heart defects. The use of *convalescent serum* in the early stages of pregnancy for those who had not had rubella was a suggested prophylactic measure.

**Asphyxia**—Methods of treating asphyxia of the newborn has been evaluated by Litchfield.<sup>89</sup> Approximately 2 per cent of all newborn babies have some difficulty in breathing. About half of this number never breathe because of permanent injury to some vital organ. The others, less severely harmed, depend upon the resuscitation treatment of the physician.

For mild or moderate degrees of asphyxiation, the removal of mucus and débris from the mouth and larynx by suction is important. Intubation or directed *laryngoscopy* may be necessary and this procedure aids the administration of oxygen. For the severely asphyxiated patient, the larynx was intubated and suction applied. Next the cord was clamped and *alpha-lobeline hydrochloride* injected into the umbilical cord, then the air passages were examined with a laryngoscope and mixtures of 93 per cent *oxygen* and 7 per cent *carbon dioxide* administered, with the pressure not exceeding 5 mm. of mercury. Occasionally oxygen was given alone.

In a review of the various methods of resuscitation, the author came to the conclusion that artificial respiration, applied to the baby who was breathing, was unnecessary and sometimes harmful. If the child has not breathed, such a procedure should not be used because

the unexpanded lungs have no air to expel and the procedure would cause only trauma, further exposure, and shock. The Drinker respirator seemed to be of little value for the infant who has not breathed and, for such patients, it was difficult to maintain the proper degree of negative and positive pressure. After respiration had been established, the apparatus sometimes helped maintain the rhythm. Mouth-to-mouth breathing was often dangerous because of trauma to the alveoli. Of the drugs, alpha-lobeline had been most effective.

**Hemorrhage** — The occurrence of spontaneous intracranial hemorrhage in infants during the second to fourth week of life has been noted by Babson.<sup>90</sup> Three infants who were apparently normal at the time of birth developed symptoms of hemorrhage on the eighteenth to thirtieth day of life. No contributory factors such as disease or avitaminosis could be discovered and it was thought possible that rupture of a congenitally anomalous blood vessel in the brain might have occurred. In two of these patients, hydrocephalus developed later, apparently as a result of the scar tissue and adhesions obstructing the normal flow of the cerebrospinal fluid. In one instance, the condition became arrested and normal development took place except that the infant continued to have a large head. The other infant died during the operation of cauterization of the choroid plexus. It seems probable that the removal of blood and the free drainage of bloody spinal fluid are indicated in such patients. After the bleeding has ceased, the replacement of the fluid by air may have some beneficial effects.

**Transfusion** of newly born infants by way of the umbilical vein has been recommended by Mayes.<sup>91</sup> The method, which was relatively simple, was employed in the treatment of eighteen

premature infants and sixteen full-term infants to replace blood loss, to stimulate respiration, and to combat erythroblastosis or hemorrhagic tendencies.

**Infections**—The time at which bacteria first appear in the upper respiratory tract of newborn infants has been investigated by Torrey and Reese.<sup>92</sup> Cultures of material taken from the nose and throat of 105 infants has shown that 95 per cent were free from bacteria for the first four hours after birth. The authors believed that this was evidence that bacterial invasion usually took place after birth from the air and other environmental sources rather than from the vaginal tract of the mother during birth. From twelve to eighteen hours after birth, one third of the group of patients still had sterile respiratory tracts, but by the end of the first day of life, all had some bacteria present. The most frequent bacteria found in the early hours of life were the *Staphylococcus albus*, types of streptococci, and occasionally diphtheroids. *Staphylococcus aureus* appeared in about 10 per cent at the end of the first day and in about 89 per cent in about the fourth to ninth day. Conspicuously absent from the cultures of these nose and throat secretions in the first days of life were pneumococci, beta hemolytic streptococci, influenza and Friedlander bacilli. It seemed likely that the invasion of bacteria into the respiratory tract of infants probably took place from air-borne infections and rarely from the nose and throat secretions of the attendants. Even when the attendants had other types of bacteria in their upper respiratory tract, the infants did not develop positive cultures of this type. The authors thought it possible that mucous membranes of the mouth and nose of the newborn were incapable of harboring these organisms. It was concluded that the wearing of masks by

the attendants had little influence, therefore, upon the health of the infant and was probably an unnecessary measure.

The treatment of infants suffering from epidemic diarrhea has been discussed by Anderson and Nelson.<sup>93</sup> They call attention to such characteristics of the infection as the sudden onset of a very severe diarrhea, early evidence of toxicity, and the usually low carbon dioxide combining power of the blood. The infants are generally listless or restless, and have suffered considerable loss of weight. Hyperpnea and cherry red lips are common symptoms. The dietary treatment usually begins with the administration of *glucose* and *Ringer's solution* until the condition improves and then *Casec*, and finally *skimmed milk* may be added to the diet. *Fluid* is given *freely*, subcutaneously or intravenously, to maintain the proper balance and to aid in the correction of the acidosis. Immediate treatment of acidosis consists of administration of *soda bicarbonate* or a *sixth normal sodium lactate* solution. These types of therapy were continued until improvement was noted. It is characteristic of the epidemics that the infants often have low levels of carbon dioxide combining power without exhibiting the classical picture of acidosis and many of the patients failed to maintain high carbon dioxide levels after therapy so that constant observation was necessary. *Isolation* procedures are also necessary and emphasis is placed upon the administration of *ascorbic acid*, *thiamine chloride*, and one of the *sulfonamides*.

*Purulent parotitis* in the newborn has been observed in five infants by Sanford and Shmigelsky.<sup>94</sup> A total of sixty-two such cases has been reported in the literature but the authors believe that the condition was more common than the reports lead one to believe. In their

experience the condition had occurred in 1 in every 2000 infants, but the incidence had been estimated by others as 1 in approximately 20,000 deliveries. *Staphylococcus aureus hemolyticus* was the etiologic agent found most frequently but such organisms as *Streptococcus*, *B coli*, and others have also been reported. The condition seemed to occur slightly more frequently in premature infants than in others but no other predisposing causes could be found. It seemed likely that the infection could enter either by way of the mouth or through the blood stream. The symptoms consisted of an elevation of temperature, generally at the end of the first week of life, a leukocytosis, and, twenty-four hours later, swelling of the parotid gland. The gland generally increased in size and became fluctuant within three or four days. Occasionally, the other parotid or the local cervical nodes became involved. The treatment consisted of the administration of *sulfathiazole*, which seemed to the authors to be the drug of choice, and simple incision of the gland when fluctuation occurred. In the past the prognosis had been considered rather poor with a mortality rate of 35 to 50 per cent, but in recent years the recovery occurred in all.

*Sulfathiazole ointment* has been used for the prevention and treatment of *pyoderma* of newborn infants by Weymuller and Ittner.<sup>95</sup> They prepared an ointment of 5 per cent *sulfathiazole* in an emulsion of oil and water which was used routinely in the care of newborn infants. Immediately after birth, the infant's skin was cleansed with *sterile corn oil*, followed by the application over the entire body of 50 gm. of the *sulfathiazole* ointment. Twelve hours later, a soap and water bath was given and thereafter the infant was treated as usual with daily baths. Whenever a

case of pustular eruption developed, the patient was isolated and treated by opening the pustules under 70 per cent alcohol and applying the *sulfathiazole* ointment. All exposed infants likewise were given another treatment over the entire body with the *sulfathiazole* ointment. This procedure has been followed in more than 3000 infants over a two-year period and only 4 sporadic cases of *pyoderma* occurred. There was no indication that the ointment produced local irritation or any sensitization of the patient to subsequent therapeutic doses of *sulfathiazole* drugs. A series of forty-three patients who had received the routine treatment in infancy was admitted to the hospital several months later and treated with *sulfathiazole* without the occurrence of any type of reaction.

*Pneumococcus meningitis* in the newborn infant is a rare but frequently fatal disease. In a patient reported by Hogg and Bradley,<sup>96</sup> recovery took place following the use of *sulfadiazine*. The condition is often difficult to diagnose in the early age period because of the absence of the typical symptoms of meningitis. Fever, convulsions, and possibly a bulging fontanel are the most typical symptoms, but rigidity of the neck, Kernig's and Brudzinski's signs, which usually accompany the disease in the older children, are likely to be absent. A total number of twenty-eight cases has been reported in the literature previously and all but two had died. The case reported by the authors was the twenty-ninth case, and the third recovery.

*Jaundice* which appears early after birth resembles erythroblastosis in some respects. Among 10,000 births, Halbrecht<sup>97</sup> found only 9 cases of true erythroblastosis. In the same group of newborn infants there were 60 other infants who were jaundiced during the first twenty-four hours after birth, and

the bilirubin content of the placental blood of these patients averaged 1.75 mg. per cent as contrasted to an average of 0.75 mg. in those with physiologic icterus and 0.55 mg. in those without icterus. These infants had no enlargement of the liver and spleen and followed a normal course, gaining weight and nursing as normal infants. It occurred to the authors that there might be some other incompatibility among blood groups than that caused by the Rh factor. Among a series of fifteen such infants, 95 per cent of the cases were incompatible with the mother, the infant in each case being type A or B and the mother type O. This incompatibility occurred three times more frequently than in the normal newborn. The author felt that some of these agglutinins against type A or B might be responsible for the early jaundice, and he employed the term "icterus praecox," signifying a condition in which iso-hemo-agglutinins, anti-A and anti-B, had passed from the mother to the child by way of the placenta.

**Nutrition**—The occurrence of *beriberi* in a newly born infant was strongly suspected in the patient observed by Van Gelder and Darby.<sup>98</sup> Immediately after birth, this infant became cyanotic and required the administration of oxygen. The heart was greatly enlarged and beat rapidly, but after *thiamine hydrochloride* was given considerable improvement took place. The mother's diet was found to have been grossly inadequate and tests performed upon her at the time of delivery indicated that she was deficient in thiamine, although she had shown no definite symptoms of avitaminosis throughout the prenatal period.

**Prematurity**—Recent observations of the nutrition and metabolism of premature infants have been summarized by Gordon and Levine.<sup>99</sup> In respect to

water exchange, an amount of 130 to 170 gm. of water per kilogram seemed adequate for both the premature and the full-term infant. When the amount was reduced from 170 to 130 gm. per kilogram, the infants were not affected but the urine became concentrated. When the fluid intake declined to between 74 to 85 gm. per kilogram, the infants developed fever. The premature infant especially seemed unable to lose heat through the skin by water evaporation when such a small amount of fluid was introduced, with the result that the temperature of the body rose. That the premature infant's kidneys were less able to concentrate urine was demonstrated by lower values of urea clearance tests. In respect to energy exchange, it was noted that premature infants had lower than average basal metabolic rates and that they were considerably less active than full-term infants. However, there was considerable variation in their basal metabolism, which emphasized the need for feeding each infant as an individual patient with no need to increase too rapidly his caloric intake. It seemed advisable to reduce the fat content of the diets because premature infants merely excreted the excessive amounts of fat which were not used. Nitrogen, on the other hand, was well handled and protein could be increased considerably in diets of premature infants. In some instances, the protein content of the diet was increased three or four times above the normal amounts and the infants continued to absorb 90 per cent of the intake. As a rule, 5. gm. of protein per kilogram of body weight could be given to premature infants, an amount three times that usually offered to ordinary full-term infants without any disturbance of digestion. The only benefit of such a high protein diet, however, seemed to be



a slight increase in the rate of growth. Carbohydrate likewise was well tolerated by premature infants. Calcium is very essential to the premature infant and the diet should include more than has generally been considered necessary for the mature patient which indicates that more is required than is present in human milk. Vitamin requirements of the premature infant are also high. Vitamins A and D are necessary in large amounts and vitamin C in doses of at least 100 mg. a day is needed to insure complete digestion of the large amounts of protein in the diet. The authors emphasized the fact that there are considerable variations among infants, especially those born prematurely, and those who are undernourished or sick. It was suggested in conclusion that human milk which has been considered the food of choice for the premature infant for many years, is deficient in calcium, phosphorus, and protein and has too high a fat content for the premature infant. Cow's milk, from which a part of the fat has been removed, has been used as the basis of mixtures successfully employed in the feeding of premature infants.

In premature infants, the stores of vitamin A are smaller than in newborn

infants and the absorption of the vitamin takes place less readily. Henley, Dann, and Golden<sup>100</sup> tested the rate of absorption of vitamin A in ten premature and in ten newborn infants and found that four of the premature, and two of the mature, infants had poor rates of absorption of the vitamin. There was a tendency for the premature infants to absorb fat less well than full-term infants. In a group of eighty-nine premature infants tested in the third week of life it was found that the vitamin A content of the plasma varied over a wide range, greater than that generally exhibited by full-term infants. Those who had received the vitamin as a supplement to their diet had higher levels than those who had not. In the examination of the liver of full-term and premature infants who had died, it was found that the full-term infants had much greater stores of the vitamin than had the premature infants. They concluded therefore that vitamin A was highly essential as a supplement to the diet of premature infants. After the first few weeks of life, the vitamin A content of the plasma was related more definitely to the intake of vitamin A than to the weight of the infants.

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## NUTRITION

NORMAN KENDALL, M.D.

### Infant Feeding

A product consisting of evaporated milk containing all necessary vitamin supplements for adequate growth has been prepared by McCollum and Grubb.<sup>101</sup> The vitamin and mineral content of the final product is shown in Table I. The evaporated milk is used for the preparation of the formula in the usual manner:

Dilution with water and addition of carbohydrate.

This product has been fed to a group of infants who received only the formula and plain bleached cereal, free of supplementary vitamins. The administration of any supplementary vitamins was forbidden. The majority of the infants were observed for not less than five months.

TABLE I  
VITAMIN AND MINERAL CONTENT OF THE TEST FOOD

<i>Ingredient</i>	<i>Calculated Amount Added Per Can</i>	<i>Amount Per Can Determined by Analysis</i>
Vitamin A . . . . .	1,500 U.S.P. units	2,480 U.S.P. units
Vitamin D . . . . .	500 U.S.P. units	500 U.S.P. units
Vitamin B <sub>1</sub> . . . . .	1,000 U.S.P. units	1,070 micrograms
Vitamin C . . . . .	120 mg.	86 mg.
Vitamin B <sub>2</sub> . . . . .	1,500 micrograms	3,600 micrograms
Biotin . . . . .	None	15.2 micrograms
Pantothenic Acid . . . . .	None	3,083 micrograms
Iron . . . . .	10 mg.	9.3 mg.
Copper . . . . .	2 mg.	4.4 mg.
Manganese . . . . .	2 mg.	1.23 mg.

(McCollum, E. V. and Grubb, W.: Am. J. Dis. Child. 68: 231 (Oct.) 1944.)

During this period, roentgen and clinical studies were obtained.

The infants thrived; the weights and measurements for the group compared favorably with accepted standards. Roentgenologic studies failed to reveal rickets or scurvy in a single case. Chemical studies of the blood for hemoglobin, serum calcium, serum phosphorus, serum phosphatase, vitamin C, and vitamin A were normal. Urine determinations for thiamine and riboflavin revealed values which were considered within normal limits. It is concluded that the test food is a suitable complete food for infants for at least the first nine months of life and that it will support normal growth and development and will prevent vitamin deficiency.

**Parenteral Feeding**—A means for the supplying of all essential nutrients by the intravenous route has been a desired aim for many years. Helfrick and Abelson<sup>102</sup> describe the intravenous administration of all major food constituents in adequate quantities to a five-month-old infant suffering with congenital megacolon, complicated by marasmus. The parenteral feeding was designed to obtain 58 per cent of the calories from

carbohydrates, 12 per cent from amino acids, and 30 per cent from fat. The preparations employed consisted of 150 cc. of 50 per cent glucose, 150 cc. of 10 per cent amino acid solution, and 180 cc. of 10 per cent fat emulsion. The fat preparation consisted of olive oil and lecithin in a 2:1 ratio suspended in water. This material was passed through a dairy homogenizer and treated for sixty minutes by supersonic irradiation so that the fat globules did not exceed 1 to 2  $\mu$  in diameter. A total of 520 calories was administered daily for five days by continuous intravenous drip. No food or water was given orally during this period.

Toward the end of the period, the baby was more vigorous; the fat pads of the cheeks had returned, the ribs were less prominent, and the general nutritional state was much improved. The authors are of the opinion that total feedings by vein are practical and can be utilized as a lifesaving procedure.

**Self-demand Feeding Schedule**—The self-demand schedule in breast feeding has become increasingly popular; the advantages given are those of a better psychologic and physiologic relation-

ship between mother and infant. Trainham, Pilafian, and Kraft<sup>103</sup> present the case history of a pair of twins, breast fed according to their own demands. During the first few weeks there was very little regularity of the feeding intervals, but after the eighth week a fairly regular four-feeding schedule per day predominated. One of the twins adopted a three-feeding day schedule after the twelfth week and the other twin after the sixteenth week. Milk from a cup was substituted for a breast feeding at the thirty-second week of life and the twins were completely weaned by nine and ten and one-half months of age respectively. Supplemental foods were introduced into the diet beginning with cereal at two months of age. Growth and development progressed at the normal rate. The authors contend that under the regime, both babies seemed to feel secure, happy, and contented, and there was a minimal amount of crying.

Simsarian and McLendon<sup>104</sup> provide additional data concerning a self-demand schedule in infant feeding. In this instance, the baby was placed in the mother's room while still in the hospital. During the latter part of the first week as many as eleven feedings in twenty-four hours were given. By the eighth week a six-feeding schedule per twenty-four hours was established, fairly regular during the daytime but irregular at night. The longest period of sleep was usually after the 6 or 7 P. M. feeding. By the tenth week a fairly regular five-feeding-per-day schedule was established. The period of observation extended until the infant was twelve weeks of age. The gain in weight was normal. The authors present a plea for placing the infant with the mother immediately following birth so that a more intimate relationship may be established soon after birth.

Gordon and Levine<sup>105</sup> in a review of metabolic studies in premature and full-term infants, stress the wide variability in the requirements of both breast and artificially fed infants.

Water retention averages about 65 per cent of the total weight gain, irrespective of whether the feeding consists of human or cow's milk. Reduction in fluid intake from average levels of approximately 170 to 130 gm. per kilogram of body weight did not lower the water balance or the loss of water through feces and skin and lungs. The urinary output, however, fell markedly. Negative water balances and the development of fever resulted when the fluid intakes were reduced to 74 to 85 gm. per kilogram. An assessment of renal function in infants reveals that the average clearance of 15 cc. per square meter per minute, with a range of from 5 to 24 cc. for prematures, is less than the 20 cc. found for full-term infants. In both instances, the clearances are less than the average of 38 cc. reported for older children. Thus, the newborn, either premature or full-term, is handicapped in respect to renal function.

Data on the energy exchange of premature, normal, and marasmic full-term infants are presented in Fig. 6. The difference in calories between the dotted line representing the normal caloric intake (120 per kilogram) and the height of the columns representing the total caloric output is the energy quota available for growth. It is evident that some infants will gain weight, some will remain stationary, and still others will lose weight on this fixed intake. The explanation of the differences in energy expenditure in the three groups of infants clarifies the need for individualization of feeding within each group. The intake of 120 calories per kilogram of body weight for prematures is usually suffi-

cient. The active wiry full-term infant may have both higher basal and activity requirements than the obese, sluggish infant. In addition, hunger and crying will further raise the energy requirements for activity, and the caloric intake may even become more deficient for growth. Satiation of appetite actually decreases the caloric output of such an infant. The marasmic infant requires higher caloric intakes because his basal

calories per kilogram as fecal fat in one third of the observations. Qualitative alterations in dietary fat of human milk, cow's milk, and cow's milk mixtures, in which olive oil replaced the butterfat, had no effect on the heightened fecal loss of fat. Quantitative reduction of dietary fat, on the other hand, consistently led to diminished excretion of fecal fat. Premature infants who do not gain on cow's milk mixtures usually fail to

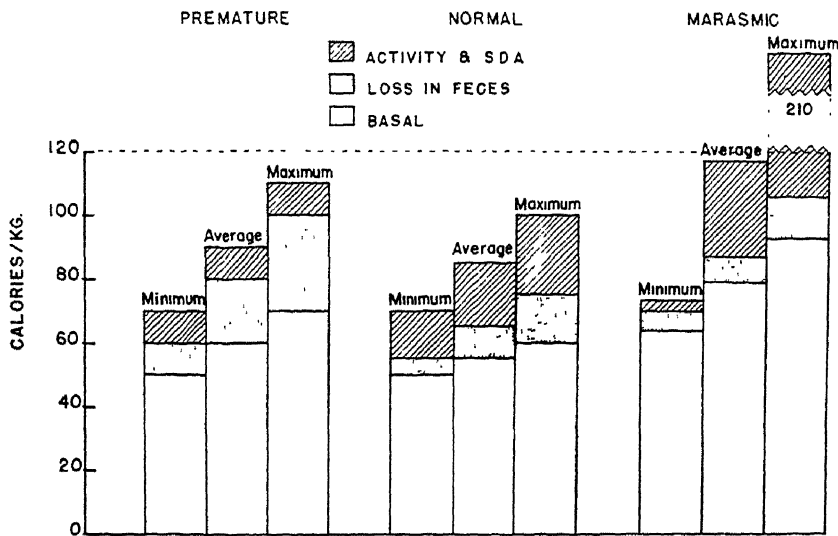


Fig. 6—Approximate energy expenditures of normal, premature, and marasmic infants. (Gordon, H. H. and Levine, S. Z.: *J. Pediat.* 25: 465 (Dec.) 1944.)

metabolism per unit of body weight is notably higher than the normal infant.

Studies of fat excretion reveal that premature infants absorb fat rather poorly in comparison with full-term infants. Such data are presented in Figs. 6 and 7.

The study consisted of forty-eight observations on premature infants and ten observations on full-term infants. The fecal caloric loss was less than ten calories per kilogram in only 21 per cent of the observations on premature infants as against 83 per cent for the observations on full-term infants. Moreover, the premature infants lost more than 20

do so because of excessive loss of calories as fecal fat. Dietary calories should not be increased; dietary fat, rather, should be reduced.

The capacity of premature infants to absorb and retain nitrogen is adequate. The nitrogen from cow's milk is absorbed as efficiently as that from human milk. The evidence suggests that the heightened retentions of nitrogen in young infants are related to their increased rate of growth.

Other metabolic studies revealed that human milk failed to meet the calcium, phosphorus, and nitrogen requirements of the premature infant. Cow's milk,

however, contains sufficient quantities of these constituents to cover the increased needs of the premature infant.

Premature infants require relatively greater amounts of vitamin A and D than do full-term infants and it is recommended that *ascorbic acid* be added to the diet of the premature infant shortly after birth. The excretion in the urine of incompletely oxidized aromatic amino acids is prevented by the administration of ascorbic acid.

**Acidosis**—According to Darrow, Da-Silva, and Stevenson,<sup>106</sup> the feeding

tion, does not induce acidosis when fed to premature infants because of a different electrolyte composition.

**Vitamins**—As chocolate milk is often employed as a substitute for whole cow's milk, an investigation of the vitamin content of such a product seems important in the present-day field of nutrition. Holmes, Jones, Wertz, and Mueller<sup>107</sup> determined the ascorbic acid, riboflavin, and thiamine content of freshly made chocolate milk. The average riboflavin content of the chocolate milk and of whole milk is similar but chocolate milk

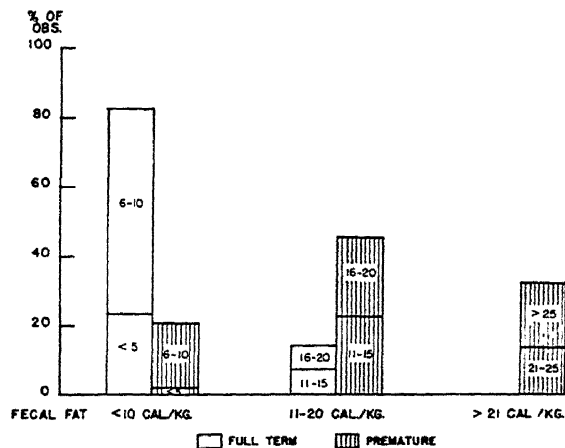


Fig. 7—Excretion of fat by young full-term and premature infants. (Gordon, H. H. and Levine, S. Z.: J. Pediat. 25: 465 (Dec.) 1944.)

of protein milk preparations induces profound symptoms of acidosis in premature infants. Metabolic studies in five prematures revealed that the acidosis results from a retention of chloride and that it may be prevented by the addition of *sodium bicarbonate* to the mixture. The acidosis was characterized by low pH, low bicarbonate, and usually high chloride levels in the serum. The retention of chloride seems to be related to the relative deficit of sodium, which makes excretion of chloride difficult. Apparently the protein milk powders contain excess chloride in relation to sodium. Hi Pro, a dried protein milk prepara-

contains definitely less ascorbic acid and thiamine than does whole milk. This study also revealed that chocolate milk made with American process cocoa is superior, as a source of vitamins, to chocolate milk made with Dutch process cocoa.

The previous studies by Rhoads, Rapoport, Kennedy, and Stokes<sup>108</sup> have been extended to include observations on 233 children. Of this group followed through two years of age, there remained 208 at three years of age, 153 at four years, and 53 at five years of age. The children were divided into four experimental groups for the purpose of

determining the adequacy of vitamin D in irradiated evaporated milk (135 U.S.P. units per reconstituted quart) as compared with accepted dosages of cod liver oil. The study also undertook to answer the question whether additional vitamin A and vitamin B complex are necessary or beneficial for satisfactory progress of the preschool child when evaporated milk constitutes the entire milk supply in his home diet. The study included data of body weight and length, head circumference, crown rump length, chest breadth and circumference, and pelvic breadth. Such developmental data as age at standing with support, walking alone, and eruption of teeth were compiled. Dental examinations to determine the incidence of dental caries, and psychometric tests were performed. Determinations of hemoglobin and serum proteins and roentgenologic examinations of the left wrist were made.

*Group I*—Eighty children received 110 U.S.P. units of vitamin D daily in the form of irradiated evaporated milk.

*Group II*—Seventy-three children received nonirradiated evaporated milk plus three teaspoonfuls of cod liver oil daily. (1500 U.S.P. units of vitamin D and 15,000 U.S.P. units of vitamin A.)

*Group III*—Forty-one children received 110 U.S.P. units of vitamin D daily in the form of irradiated evaporated milk plus 10 drops of carotene equivalent to approximately 2250 U.S.P. units of vitamin A.

*Group IV*—Thirty-nine children received 110 units of vitamin D daily in the form of irradiated evaporated milk plus 10 drops of carotene and one half tablespoonful of brewer's yeast powder daily, which furnished approximately 0.5 mg. thiamine and 0.2 mg. riboflavin.

The study demonstrated that evaporated milk was nutritionally adequate as a continuous milk food for the growing

child. The incidence of infections was approximately the same for all groups, indicating that the administration of carotene had no beneficial effect. There were no significant differences between the various groups in respect to the anthropometric data, indicating no apparent beneficial effect of the vitamin supplements upon the growth process. There was no clear-cut evidence of benefit on the mental and physical growth from the addition of vitamin B complex to the diets of the children. No instance of marked rickets occurred in any of the children but bone changes diagnosed on the roentgenogram as mild rickets occurred in 13.3 per cent of the entire group. In most cases, the roentgenologic diagnosis was not confirmed by clinical findings. No appreciable difference was found in the antirachitic effectiveness of 1500 units of vitamin D in the form of cod liver oil as compared to 110 units of vitamin D in irradiated evaporated milk. Incidence of dental caries in all groups was low for the age level studies. The study may indicate the importance of a continuous source of vitamin D as a factor in reducing the incidence of caries.

**Vitamin A**—An investigation of the absorption, storage, and requirement of vitamin A by premature infants was conducted by Henley, Dann, and Golden.<sup>100</sup>

Employing the standard vitamin A absorption test, four of ten premature infants showed extremely poor absorption of vitamin A during a period of five hours. The absorption of vitamin A by the other six of the group was within normal limits. No infant over twenty-one days of age weighing more than 2300 gm. showed poor absorption. A comparable group of mature infants were studied and were found to absorb the vitamin more efficiently. Apparently both age and prematurity influence the

efficiency of absorption of vitamin A. The retention and excretion of fat were also studied and a direct parallelism between absorption of fat and absorption of vitamin A from the intestinal tract was found.

Levels of vitamin A in the plasma of eighty-nine premature infants on approximately the twenty-first day of life were determined. The mean values for forty-four infants who weighed less than 2000 gm. at birth and for forty-five infants whose birth weights were 2000 gm. or more were 11.4 and 12.3 units, respectively. There was a significant difference in blood vitamin A levels between the infants who received no vitamin A concentrate and those who received various vitamin A supplements; the former averaged 8 units and the latter 14.7 units. The livers removed at autopsy of premature and mature infants were assayed for vitamin A. Without exception, those of the mature infants contained almost twice as much vitamin A as those of the premature infants.

These studies suggest that the administration of vitamin A should be started early in the life of premature infants because they have relatively low reserves of vitamin A in the liver and are apt to absorb dietary fat and vitamin A poorly.

**Vitamin B**—Congenital beriberi is an extremely rare disorder. A newborn infant who was suspected of having congenital beriberi and who promptly improved upon the administration of large doses of thiamine is reported by Van Gelder and Darby.<sup>110</sup> The infant became cyanotic three hours after delivery. Examination revealed a hoarse cry, a very rapid pulse, and an enlarged area of cardiac dullness to percussion. During the first day of life, the infant suffered several cyanotic attacks. Convulsive movements occurred when the infant was thirty hours old. Twelve hours after a sec-

ond dose of 50 mg. of *thiamine hydrochloride* was given subcutaneously, dramatic improvement was noticed; the convulsions ceased, the cyanosis disappeared, and food was accepted. Roentgenogram of the chest when the infant was 18 hours old revealed an enlarged heart; at the age of twelve days, marked reduction in size in the heart was noticed. An electrocardiogram taken four days after thiamine therapy had been instituted revealed evidence of myocardial disease; at seven weeks of age, the electrocardiogram was normal. Thiamine in 50 mg. doses was administered subcutaneously every eight hours for twelve days. Investigation of the diet of the mother revealed that the food consumed during her last trimester of pregnancy was grossly deficient in thiamine. Laboratory data obtained during the postpartum period indicated a state of thiamine deficiency in the mother. The authors are of the opinion that an infant presenting extreme tachycardia and enlarged heart should be treated with large doses of thiamine hydrochloride as a therapeutic test. No untoward effects of the large doses of thiamine were noticed in this instance.

**Vitamin D**—Dunham and Thomas<sup>111</sup> studied a group of ten children who in early childhood had shown evidence of severe rickets with a view to determine the effect of early rickets on skeletal development.

Five children of the group had rachitic pelves in adolescence. Three with rachitic pelves were more than four years of age when active rickets was diagnosed in contrast to the fact that four of the children whose pelves were normal were less than three years of age when active rickets was diagnosed. Apparently, the later active rickets is present, the greater is the chance that

the pelvis will show rachitic deformities in adolescence. All of the ten children had some deformity of the lower extremities during adolescence. Knock-knees were associated more often with rachitic deformities of the pelvis than were bowlegs. Evidence is presented which suggests that if knock-knees were

present in early childhood the pelvis in adolescence is more likely to show the deformities of rickets than if bowlegs were present in early childhood. High ratios of sitting height to standing height were found for all but one of the children, indicating retardation of growth of the lower extremities.

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## PARASITIC DISEASES

NINA A. ANDERSON, M.D.

In a survey designed to study the incidence of intestinal parasitic infestation, Brown<sup>112</sup> demonstrated 646 specific parasites in 512 children between the ages of six weeks and twelve years. The percentage frequency with which the different parasites were found was: *Entamoeba histolytica*, 8.0; *Entamoeba coli*, 35.2; *Endolimax nana*, 30.5; *Dientamoeba fragilis*, 3.9; *Iodamoeba buetschlii*, 1.4; *Giardia lamblia*, 32.2; *Chilomastix mesnili*, 5.1; *Retortamonas intestinalis*, 2.3; *Trichomonas hominis*, 1.4; *Ascaris lumbricoides*, 0.6; *Enterobius vermicularis*, 4.1; *Trichuris trichiura*, 0.4, and *Taenia* sp., 1.2.

In a correlation of symptomatology with enterozoic parasitism in 345 children, Brown<sup>113</sup> found specific symptoms of only 7.7 per cent of the surveyed parasites. Seven of the forty-one children with *E. histolytica* had acute moderately severe, nonfulminating dysentery, their stools containing microscopic blood. Each child had intermittent constipation and diarrhea, tenesmus, and malnutrition. There was generalized abdominal tenderness which was accentuated over the right iliac fossa. Eleven children had a history of chronic recurrent diarrhea; nine of them were underweight. Twenty-three were carriers without symptomatology, and thirty-four had

symptomatology not directly ascribable to parasitism. *Emetine*, *carbarsone*, or both, gave satisfactory clinical results.

*E. coli*, *E. nana*, *D. fragilis*, and *I. buetschlii* were rarely responsible for symptoms, although there was gastroenteritis in cases with hyperparasitism.

Of the 165 patients with *G. lamblia*, 15 had acute generalized abdominal aches and pains, intermittent mild diarrhea, or constipation. Three had stools containing excess mucus and detectable blood. All of the 15 patients were irritable, inattentive, and had moderate flatulence. Only one had significant hyperparasitism. Appropriate dosages of *atabrine* relieved the acute symptoms and removed or decreased the number of *G. lamblia*.

Two of the three children with *A. lumbricoides* had generalized abdominal aches and tenderness with episodes of rather colicky epigastric pain and had moderate malnutrition. *Caprokol* (hexylresorcinol) relieved the symptoms.

Twenty of the twenty-one patients with enterobiasis had pruritus ani with disturbed sleep, irritability, and inattentiveness. They responded to appropriate doses of *gentian violet* and protection from reinfection from contaminated fingers.



The two children with *T. trichiura* had excessive mucus in the stools, a tender colon, periodic diarrhea, anemia, and malnutrition. *Caprokol* relieved the symptoms.

Four of the six patients with teniasis had flatulence, intermittent constipation and diarrhea, abdominal tenderness, erratic appetite, and malnutrition. The fifth was malnourished and the sixth patient had symptoms referable only to a nasopharyngitis. *Male fern* was efficacious in the treatment of all of these cases.

Acute gastroenteritis was present in only 0.9 per cent of the parasitized cases as compared with 41.3 per cent of the nonparasitized which were studied. Acute and recurring upper respiratory infections were more frequent in parasitized children.

### Ancylostomiasis

Miller, Einhorn, and Whittier<sup>114</sup> have observed seventy-one patients with un-mixed ancylostomiasis, all of whom came to the hospital with other diseases and the helminth infection was discovered by routine examination of the stool. Even in the anemic patients, no subjective symptoms were noted until the anemia reached such a degree that critical heart failure supervened. The leukocytosis, when present, was accounted for by associated unrelated infections; the differential leukocyte count was normal. *Hexylresorcinol* was considered a good ankylostomacide and somewhat less toxic than *tetrachlorethylene*. In some instances, both drugs were used with most satisfactory response. *Oil of chenopodium* was less satisfactory. *Iron* and *blood transfusions* were needed to combat anemia.

### Ascaris Lumbricoides

In a clinical survey of 125 cases of ascariasis in children in Panama, Ein-

horn, Miller, and Whittier<sup>115</sup> found a relatively high frequency in early life, with 52.8 per cent of the cases occurring in children under the age of four years. Most of the patients came to the hospital for diagnosis and treatment of other diseases, of which malaria and secondly respiratory infection were the most frequent. The most frequent symptoms of ascariasis were the passing of worms by bowel and vomiting. Abdominal pain, anorexia, diarrhea, and malnutrition were encountered less frequently. Disturbances of the central nervous system were seen infrequently; convulsions occurred in six patients, in four of whom there was no disease other than ascariasis. Among a total of thirty-five appendectomies performed during the period of the study, none of the appendices contained ascarides. The hemoglobin level and the erythrocyte count did not differ materially from those of the control group. Deviations from the normal leukocyte count were caused by unrelated coexisting diseases. Eosinophilia did not occur frequently.

*Oil of chenopodium* was given to eight patients, the doses varying with the age of the patient. *Magnesium citrate* was administered at 11 A. M. on the day before treatment was to begin. Breakfast was withheld on the following day and the drug was given at 6 A. M. and was followed in two hours by a second dose of the purgative. Food was withheld until after brisk catharsis had occurred. Vomiting occurred in four patients, intestinal cramps in two patients, and prostration in two patients. In two patients infection persisted and was treated with another drug.

*Tetrachlorethylene* was used for fifteen patients in doses of 0.18 cc. (3 minims) per year of age of the patient. *Magnesium citrate* was given the night before treatment was to begin,

breakfast was withheld the following morning, and the measured amount of vermifuge administered under a layer (a full dose) of solution of magnesium citrate. The untoward symptoms were vomiting, abdominal cramps, and prostration. On this schedule, tetrachloroethylene was not effective in eradicating the infestation.

*Hexylresorcinol* was used for ninety-eight patients and seemed to be the safest, the most efficient, and the easiest to administer. The doses were 0.1 gm. per year of apparent age with a maximum dose of 1 gm. A preliminary laxative of magnesium citrate was administered at noon on the day preceding the beginning of the treatment. A light evening meal was given. On the following morning breakfast was withheld, at 6 A. M. the correct number of capsules were given as one dose, and *magnesium citrate* was given twenty-four hours afterward. If severe infection was present, an enema was given in addition to the second dose of citrate. The capsules were either swallowed whole with water or inserted directly into the esophagus by the physician. Aside from infrequent vomiting, no serious toxic symptoms were observed. To eleven patients, two courses, and to two patients three courses of hexylresorcinol were administered before the stools became negative for ova.

Treatment of the source of the infection as well as of the patient is necessary, and prevention of the disease cannot be accomplished until sanitary disposal of feces has been provided.

### **Dientamoeba Fragilis**

From studies on the incidence and the possible pathogenicity of *Dientamoeba fragilis*, Knoll and Howell<sup>116</sup> concluded that this ameba is pathogenic for man. Soft unformed stools with much undi-

gested food frequently contained *D. fragilis*, and stools containing this parasite were greenish brown in color and had a characteristic foul odor. In direct smears *D. fragilis* appeared as a small ameba with one or two nuclei and clear transparent cytoplasm. There were variations in size and the ameba were more actively motile in culture than in direct preparation. They were easily recognized in saline preparations from fresh liquid stools or from a culture of infected stools, and they grew readily on all ordinary media used for other ameba. The incidence was approximately the same in males and in females. Many of the patients had no clinical manifestations, and others complained of such symptoms as headache, nausea, loss of appetite, abdominal pain, gas, alternating diarrhea and constipation, and malaise. There was a gradation of symptoms up to acute gastrointestinal attacks that simulated severe infection with *E. histolytica*. Clinical symptoms of persons harboring *D. fragilis* as the only parasite improved quickly after the administration of *carbarsone*, which also cleared the stools of the ameba.

### **Enterobius Vermicularis**

In a survey of 200 consecutive cases of oxyuriasis in children in the Canal Zone, Miller and Einhorn<sup>117</sup> noted a low incidence of the infection in infants under two years of age. There was equal sex distribution in this series. Almost all of the hospitalized patients had disease unrelated to oxyuriasis and 75 per cent. of them were free from subjective symptoms attributable to the oxyuriasis; in the group from the outpatient clinic, oxyuriasis was often the only disease present and symptoms were encountered in 50 per cent of the group. The symptoms which were encountered included:

TABLE II

	Percentage of Patients	
	Group 1*	Group 2†
Local symptoms and signs:		
Worms on anal region.....	13	59
Pruritis ani and associated sensations.....	0	17
Vaginitis, nonspecific .....	1	1
Symptoms secondary to local discomfort:		
Wakefulness at nights.....	1	7
Enuresis .....	0	3
Burning on urination.....	1	0
Nocturia .....	0	1
Pain in groin caused by inguinal adenitis secondary to vulvovaginitis	1	0
"Nervous" symptoms probably secondary to disturbed sleep and general discomfort:		
Anorexia .....	6	7
Failure to gain weight.....	6	1
Irritability, fretfulness, restlessness.....	3	3
Lethargy .....	2	1
Grimacing, facial tics.....	1	1
Thumb sucking .....	0	1
Gritting of teeth .....	0	1
Headache .....	0	1
Gastrointestinal symptoms probably due to irritation by enterobii within the gastrointestinal tract:		
Abdominal pain .....	11	13
Nausea and vomiting.....	5	4
Diarrhea .....	2	1

\* Group 1—Patients from hospital wards.

† Group 2—Patients from the outpatient clinic.

(Miller, J. F. and Einhorn, N. H.: *Am. J. Dis. Child.* 68: 376 (Dec.) 1944.)

There was not a single instance of convulsions encountered in this series and the authors felt that, in the absence of irrefutable proof, pinworms should not be considered a cause of convulsions in children. Enterobii can cause inflammation in the appendix, but there was no evidence that pinworms alone could cause the suppurative form of the disease. Malnutrition, anemia, and allergic manifestations did not occur with unwarranted frequency.

The diagnosis was established in most instances by seeing worms on the perianal region or by collecting them or their ova on a cellophane tip. Examination

of stools or of stool concentrates was not of as much value.

There are no significant differences in hemoglobin level and erythrocyte counts between the children with oxyuriasis and a control group. Deviations in the leukocyte counts were caused by unrelated coexisting disease. Eosinophilia was not frequently encountered.

*Gentian violet* appeared to be the best of the methods of treatment. Its use is limited, however, to the children old enough to swallow the capsule intact, and occasionally there is intolerance manifest by vomiting. Enteric-coated capsules were used, in doses of

from 0.015 gm. (0.25 grain) to 0.06 gm. (1 grain) three times a day twenty minutes before each meal for two periods of eight days each, interrupted by a rest period of seven days.

*Quassia enemas* relieved the symptoms, but they did not always cure the infection, and they were troublesome for the mother. Rectal injections of 60 to 90 cc. (2 to 3 ounces) of a strong infusion of quassia chips were given, followed in twenty minutes by a soapsuds enema. This routine was repeated on alternate days for two months.

In their experience, *tetrachlorethylene* was of no value when administered as a single dose, preceded the night before by a preparatory purgative of magnesium citrate. The tetrachlorethylene was administered at 8 A. M. with another dose of magnesium citrate, food being withheld until supper.

With each type of treatment, specific

instructions regarding prevention of self-reinfection were given: Fingernails were to be cut and ammoniated mercury ointment was applied to the fingers and to the anal region twice daily.

### **Trichuris Trichiura**

In a survey in Panama, Getz<sup>118</sup> found that 7.6 per cent of the group studied were infected with *Trichuris trichiura* as a single parasite or in combination with other intestinal parasites. Although the general impression is that this is a relatively harmless parasite, serious symptoms and physical signs may result. Four patients with massive infections of *T. trichiura* died. Three of them had prolonged diarrhea. All four of them had emaciation, fever, abdominal distention, anemia, and cardiac dilatation. In one case there was prolapse of the rectum. One of the patients had acute hemorrhagic nephritis.

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## **PERTUSSIS**

RICHARD E. WOLF, M.D.

Sako, Treuting, Witt, and Nichamin<sup>119</sup> undertook a study of the reaction of young infants three months of age or younger to parenteral injection of alum-precipitated pertussis vaccine. The material used contained forty billion bacilli per cubic centimeter. The alum-precipitated vaccine was given in dosage of 0.2 cc. for the first injection, 0.3 cc. for the second injection, and 0.5 cc. for the third injection for a total of 1 cc. No interval between injection is specified. The data showed that these young infants tolerated the injections well. The incidence of local reaction was 8.6 per cent of 6600 injections. Abscess formation occurred in 0.6 per cent. These abscesses were sterile and not associated

with a febrile reaction or discomfort. Seventy-four per cent of the local reactions were mild and characterized by local redness and induration up to 2.5 cm. in diameter. Only 1.8 per cent were severe, characterized by induration and redness greater than 5 cm. in diameter. Local reactions followed the second and third injections more frequently than the first injection. Systemic reactions were reported following 467 (7.1 per cent) of 6600 injections; 3.4 per cent of these were severe and 77.5 per cent were mild. A peculiar paroxysmal cough, resembling that of pertussis, occurred with sufficient frequency to be considered related to inoculation. It began shortly after injection and disappeared rapidly.

Data on the immunologic response of these young infants as measured by agglutination tests were collected. The rapid agglutination test (Lilly) was used throughout this study. The greatest number of positive reactions was found between the third and fourth month after completion of the immunization. Twenty-four months after completion of the injections, 63 per cent of infants tested still gave positive reactions. Seventy-five per cent of these very young infants exhibited antibody response as measured by the test.

The authors conclude that it is a safe as well as a practical procedure to begin immunization against pertussis in the early months of life instead of waiting until after the seventh month as has been customary. In this way infants may receive protection against the disease during the age period when the mortality rate is highest.

Turnbull<sup>120</sup> proposes the hypothesis of synergy of two antigens to explain the improved immunization response he noted when alum-precipitated diphtheria toxoid was given to children exposed to pertussis. He suggests that diphtheria toxoid be given during the incubation period and repeated at weekly intervals. In sixty-one children exposed to whooping cough and inoculated with *alum-precipitated diphtheria toxoid* occurrence of pertussis was prevented.

Silverthorne, Zacks and Jenkins<sup>121</sup> report on experience gained from examining eighty-seven children for the presence of H. pertussis by means of (1) direct smear of nasal mucus, (2) culture of nasal mucus, and (3) cough plate culture.

Smears and cultures of nasal mucus were taken by means of a sterile rubber catheter inserted into the patient's nostril. A 20-cc. syringe was attached to the end of the rubber catheter and suc-

tion applied. After obtaining nasal mucus in this way, the rubber tubing was returned to a sterile test tube. A culture was then made on Bordet medium and incubated two to four days. From the nasal mucus, direct smears were made on glass slides and examined microscopically after staining by Gram's method. The cough plates were taken in triplicate and incubated two to five days.

Of the fifty-four cases of whooping cough examined, twenty-three cultures of nasal mucus were positive (42 per cent) and thirty-one were negative. Of the fifty-four cases of whooping cough, thirty cough plate cultures were positive (55 per cent) and twenty-four were negative. Of the fifty-four children who had clinical whooping cough, forty-four showed the presence of gram-negative bacilli in a direct film of nasal mucus (80 per cent).

The authors felt that direct smears of nasal mucus early in the disease are helpful in obtaining preliminary evidence in diagnosis of whooping cough. Cough plate cultures were superior to nasal mucus cultures.

Silverthorne<sup>122</sup> reports that diagnostic methods are reliable in pertussis. Contrary to the opinion of others, Silverthorne showed that cough plates were as reliable in the 0- to 2-year age group as in the 2- to 14-year group. Results of direct smears of nasal mucus from patients suspected of having pertussis are fairly reliable. Of fifty-four children with pertussis, forty-four showed the organism in direct smear of nasal mucus. Cough plates have been positive in as high as 94 per cent in the author's series.

Silverthorne recognized the value of vaccine made from culture of *Hemophilus pertussis* in phase I but he was anxious to prove that this vaccine is

actually antigenic. He found that when mice were injected intraperitoneally with *Hemophilus pertussis* in 5 per cent hog's gastric mucin, 84 per cent died as compared with 18 per cent deaths in mice injected with *Hemophilus pertussis* suspended in broth. This experiment furnished the author with a method of testing virulence of various pertussis vaccines. It has been demonstrated that immune sera produced by the injection of human beings and rabbits with phase I strains of *Hemophilus pertussis* protect mice against a fatal septicemia.

The author feels that there is a very definite place for the use of *immune serum* in immediate prophylaxis and treatment. He reports results obtained by the use of immune pertussis rabbit serum during an outbreak of pertussis in a convalescent home in Toronto. Alternate contacts were given the serum and there were no cases of pertussis in the group of ten. In a control group of eleven, there were three cases of pertussis.

Silverthorne sees no evidence that pertussis is a "toxin-antitoxin disease." He also feels that any skin test using pertussis toxin is not reliable in determining immunity or susceptibility.

*Hemophilus pertussis* was isolated in culture material obtained in one of three methods from forty out of fifty-three patients by Bullowa, Buxbaum, and Scheinblum.<sup>123</sup> The three methods were cough plate, nasopharyngeal swab, and laryngeal suction; 87.5 per cent had positive cultures from nasopharyngeal swabs, 55 per cent by laryngeal suction, and 50 per cent by cough plates.

Fifty patients were tested for the presence of circulating agglutinins. Only 14 per cent of the patients showed the presence of agglutinins.

Thus there was little correlation between the results of the cultures and

the agglutination tests. Of the thirty-eight patients tested who had positive cultures, only nine showed agglutinins.

Scheinblum and Bullowa<sup>124</sup> report on the treatment of pertussis in twenty-three patients using lyophile hyperimmune human pertussis serum. Only critically ill children were treated and serum was administered intramuscularly. Most of the patients received three 20-cc. doses, each dose dissolved in 10 cc. sterile distilled water.

Twelve of the patients treated were under three months of age and 75 per cent of these infants had a good response. There were no deaths in this group.

The agglutinin titers were determined before treatment and in no instance were there any agglutinins in the blood. Following therapy with *hyperimmune human serum*, at varying intervals, the agglutinin titers varied from 1:40 to 1:1600.

It was found that the lymphocytosis of the blood was suppressed following administration of serum.

The results in this small series showed that eighteen of the twenty-three patients treated (78.1 per cent) had good or moderately good response to therapy. In the one to three months' age group, eleven of the twelve patients had good or moderately good response.

Lapin<sup>125</sup> reports on the use of a tenfold concentrated *globulin fraction* of *human hyperimmune pertussis serum*. This material was used in prophylaxis of ten contacts to whooping cough. These contacts were between the ages of four months and thirteen years. In each case the contact was intimate, an infecting sibling, and the prophylactic injection was given before the infecting sibling had reached the paroxysmal stage. The dosage employed was two

injections of 2.5 cc. of the globulin fraction given at two-day intervals. There were no local or general reactions. Of the ten contacts, seven were completely protected and three developed a mild type of paroxysmal cough.

This material was also used in the treatment of twenty-five patients with whooping cough ranging in age from four months to thirty-one years of age. Two of these patients were under six months and twelve were from one to

five years. Eleven showed marked improvement after from one to five injections of 2.5 cc. of the globulin fraction. Seven patients showed moderate improvement and seven showed no improvement.

Thus, in the prophylaxis of contacts, 70 per cent of ten intimate, familial, sibling susceptibles were protected. In the treatment of active whooping cough, 44 per cent of twenty-five cases showed marked improvement.

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## POISONING IN CHILDREN

NINA A. ANDERSON, M.D.

### Aniline Dye

Unexpected and pronounced cyanosis and dyspnea were the principal symptoms which Graubarth, Bloom, Coleman, and Solomon<sup>126</sup> observed among seventeen infants who had aniline dye poisoning. Diapers stamped with ink containing aniline dye were accidentally sent to the nursery and used without first having been laundered and sterilized. The infants absorbed the aniline through the skin of the buttocks. Other symptoms included anorexia, irritability, weak cry, vomiting, loose stools, distention, hematuria, jaundice, and enlargement of the spleen. *Transfusions of whole blood* or of *red cells* suspended in saline solution, *removal* of the source of *poisoning*, and *fresh air* were the important therapeutic measures. *Methylene blue* (5 cc. [ $\frac{1}{2}$  grain], in each of the feedings every three hours for two days) and oxygen with 5 per cent carbon dioxide were also used. Thirteen of the infants recovered, and four died from unrelated causes. There were no reports of refractory anemia or of persistent cerebral damage.

### Hair Lacquer

Dermatitis presumably resulting from hair lacquer used by the mother has been reported in two infants less than a year of age. Plotz<sup>127</sup> states that the effect of the synthetic resins, combinations of rosin and maleic anhydride, which have been substituted for the unobtainable shellac, is enhanced by the extremely high or extremely low pH of the finished commercial product.

### Salicylates

Death resulting from the administration of relatively large doses of acetylsalicylic acid to a four-year-old child has been reported by Ashworth and McKemie.<sup>128</sup> The child had hyperpnea, hyperpyrexia, and convulsions following the ingestion of four doses of 0.17 gm. of acetylsalicylic acid at four-hour intervals. The autopsy showed degenerative changes in the liver, hyperemia, and multiple petechial hemorrhages, and it was believed that these changes were due to capillary damage and hypoprothrombinemia produced by the salicylate. This report lends additional evidence for the need of the administration of vitamin

K when large doses of salicylates are employed.

Troll and Menten<sup>129</sup> have reported four instances of salicylate poisoning. Two occurred in children who were treated with acetylsalicylic acid, another accidentally swallowed oil of wintergreen, the fourth received salicylate therapy for a long time in the hospital and later an unknown amount in his own home. The symptoms included extreme dyspnea, irritability, restlessness, nausea and vomiting, dehydration, and eventually disorientation, paralysis, coma, and death in three instances. Hyperpnea was the first outstanding symptom presumed to result from central stimulation with the salicylate acting directly on capillary endothelium, thus increasing its permeability and allowing greater diffusion of the drug. The pathologic findings were generalized petechial hemorrhages in supportive tissues and serous surfaces, cloudy swelling and fatty degeneration of the kidneys and the liver, and congestion of parenchymatous organs. **Hydration** appeared to be the most important part of the therapy. Recovery in one instance occurred after withdrawal of the drug and prompt institution of hydration. An obvious effect of hydration is dilution of the salicylate. When the patient has taken a single large dose of salicylate, gastric lavage is indicated; but if there has been no treatment until hyperpnea has developed, absorption has progressed too far for lavage to be effective.

The possibility of poisoning when large doses of salicylates are employed in the treatment of rheumatic fever is emphasized by the report of Fashena and Walker.<sup>130</sup> A nine-year-old Negro boy was given 6 gm. of sodium salicylate orally per day for a period of four days for the treatment of acute rheumatic fever. Subsequently a larger dosage

(8 gm. per day) was responsible for hyperpnea, nausea, and vomiting, followed by disorientation and hallucinations. The bleeding time was 5 minutes 30 seconds, the clotting time 10 minutes, and the prothrombin time was more than five times the normal. The carbon dioxide combining power was 33 volume per cent, and the urinary pH was five. The Gerhardt test gave a deep purple color characteristic for salicylates. There was albuminuria, and many white cells and finely granular casts were found in the urine. Recovery from the hypoprothrombinemia and the hyperpnea was rapid when **synthetic vitamin K** was administered and the salicylate therapy was stopped.

Experimental studies on six hospitalized children ranging in age from six to eleven years showed that doses as high as 0.2 and 0.22 gm. of sodium salicylate per kilogram of body weight were needed in order to achieve blood salicyl levels of 350 micrograms per cubic centimeter. After twenty-four hours on this dosage, the amount given could be reduced to 0.15 and 0.17 gm., respectively, without subsequent diminution in the blood salicyl level. These authors recommend that the Coburn treatment for rheumatic fever be controlled by repeated estimations of the blood salicyl level in order to attain maximum therapeutic effectiveness with minimum doses of the drug. Since moderate as well as large doses of sodium salicylate regularly induce hypoprothrombinemia, large doses of vitamin K are indicated to prevent the development or to hasten the correction of prothrombin deficiency. These authors also feel that the hyperpnea is the result of central stimulation by the salicyl radical. The severe hyperpnea of salicylate intoxication may be unassociated with ketosis and out of proportion to the bicarbonate deficit.



## POLIOMYELITIS

RICHARD E. WOLF, M.D.

Boines<sup>131</sup> reports on twenty-one cases of poliomyelitis receiving treatment with the *Kenny technic* (modified) and *prostigmine*. The author's modification of the Kenny technic consisted of the elimination of the hot packs and the substitution of prostigmine. Using this drug, the burdensome hot packs could be dispensed with and the relief of spasm was even more marked.

One of the most encouraging effects of prostigmine was on the old, chronic cases of poliomyelitis. A number of such cases were studied over a period of many months and found to make good responses to prostigmine.

The author states that in the future he plans to treat the majority of patients at home, using the modified Kenny technic with prostigmine. Muscle reeducation and exercise are valuable adjuncts to drug therapy.

One-half mg. *prostigmine methylsulfate*, four times a day subcutaneously in addition to 15 to 30 mg. *prostigmine bromide* orally three or four times a day over a period of 10 to 12 days, is the recommended dosage.

Lucchesi and LaBocchetta<sup>132</sup> reviewed the experience with poliomyelitis in the Philadelphia Hospital for Contagious Diseases for the years 1937 to 1942 inclusive. Four hundred thirty-two patients were admitted with the disease during this period. Careful analysis of the case material was made to determine the relationship of tonsils and adenoids to the type of poliomyelitis. The authors found that tonsils and adenoids were absent in a significantly high percentage of patients who had bulbar or bulbospondyl poliomyelitis. There were nineteen patients under six years of age who had had their tonsils and adenoids re-

moved, and eight of these children (41 per cent) had bulbar involvement. Of 161 patients, also under six years of age but who had not had adenotonsillectomy, only 13 (8.1 per cent) had bulbar involvement. There were 18 deaths in the whole series of cases and, of these, 14 (78 per cent) had had adenotonsillectomy.

Over 76 per cent of the patients with bulbar poliomyelitis and 61 per cent of those with bulbospondyl poliomyelitis had had adenotonsillectomy, while only 30.9 per cent of the patients with only spinal involvement had had their tonsils and adenoids removed. Nonparalytic poliomyelitis occurred in about equal proportions of the adenotonsillectomized and the nonadenotonsillectomized patients.

The authors believe that a positive correlation exists between absence of pharyngeal lymphoid tissue and involvement of the higher centers in poliomyelitis. They stress the fact that adenotonsillectomy need not occur within the incubation period of the disease in order to have an effect on the type of disease. It is inferred that Waldeyer's ring of lymphoid tissue inhibits the passage of the virus through the pharynx.

Perhaps by leaving tonsils and adenoids in place, the incidence of bulbar poliomyelitis may be reduced. If this is true, indiscriminate removal of tonsils and adenoids should not take place, especially in children living in communities having annual outbreaks of poliomyelitis.

Based on his own experience in institutional physical therapy, especially in poliomyelitis, Snow<sup>133</sup> presents his concepts of modern treatment of poliomyelitis. For convenience he divides the treatment into four stages:

1. **Expectant or Acute Stage**—During this stage, most attention will be directed toward establishing the diagnosis and evaluating the extent of the disease. Treatment will be largely symptomatic. This will include strict individual precautions, keeping the pharynx clear in bulbar cases, administration of fluids and carbohydrate to prevent dehydration and ketosis, oxygen if indicated, respirator when needed, tracheotomy upon indication, bolsters or small pillows to relieve muscle strain and to prevent stretch reflex irritation, and hot fomentations as pain and muscle tension indicate.

2. **The Subacute Stage**—Treatment is now directed toward the production of improvement, maintenance of nutrition, and the prevention of deformities. This treatment belongs to the field of physical therapy. Care should be taken to prevent contracture. The patient is kept flat in bed. The feet should be supported against a footboard. All poliomyelitis patients should be turned in bed several times daily. Occasionally, posterior molded shells to support the foot in dorsiflexion at all times except during periods of hot packs are helpful in preventing contracture in the extensor calf muscles. In deltoid and trapezius paralysis, the use of a sling to support the shoulder as soon as the patient is placed in the semiupright position is advisable. In the subacute stage, hot packs, as applied by Sister Kenny, are effective in producing relaxation of muscle tension. Furthermore, the warmth helps to maintain the nutrition of skin and muscles.

3. **The convalescent stage** is marked by progressive reeducation of muscles. Support may be offered by means of non-surgical orthopedic aids as wedges, shoes, and braces. Usually hot packs may be dispensed with at this stage inasmuch as the stretch reflex is no longer present. Hot packing of patients is hard labor and

expensive and should not be continued past its period of usefulness. Tendon stimulation by passive motion of a joint is helpful in the reeducation of muscles. Such muscle reeducation should be progressive and, as soon as muscle tension will permit, the patient should be allowed gradual increased activity. Weak muscles should be supported by light braces. Fatigue of muscles should be avoided.

4. **The Residual Stage**—Here orthopedic surgery offers the greatest chance for continued improvement. Stabilizing operation, muscle and fascial transplants will do much to lessen needs for crutches and braces.

Weaver<sup>134</sup> reports on eleven experiments designed to test the effects of vitamin B complex-free diets, of partial inanition, and of sex on the susceptibility of cotton rats to the virus of poliomyelitis.

Results of this work yield no evidence to indicate that vitamin B complex-free diets, partial inanition, or sex significantly affect the susceptibility of cotton rats to the virus of poliomyelitis.

Thus these results would tend to discount former theory that the virus of poliomyelitis is a biochemical by-product of vitamin B deficiency and that poliomyelitis is a fulminant form of beriberi.

The pathologic changes in posterior as well as anterior area of the spinal cord are well recognized in poliomyelitis. However, sensation seems uninvolved after the first attack of pain, according to Frohring, Kohn, Bosma, and Toomey.<sup>135</sup> In order to test sensation more accurately, a pallesthesiometer has been used. By means of this instrument, minor changes in vibratory sensibility are detectable. These changes have not been demonstrated in poliomyelitis despite the obvious pathologic changes in the posterior part of the cord and in sensory ganglions.

Although it is an accepted fact that many patients with acute poliomyelitis

excrete virus in their stool, little has been known of the duration of this excretion beyond the first four weeks of the disease. Horstmann, Ward and Melnick<sup>136</sup> undertook to study the average duration of excretion of virus in stools of patients following acute infection. Sixty patients admitted to the New Haven Hospital were studied. Immature rhesus monkeys were used as test animals. Their results showed that 50 to 60 per cent of the patients were found to excrete virus in the first four weeks of the disease. At five to six weeks only 27 per cent of the specimens tested were still positive and at eight weeks only 12.5 per cent of the specimens were positive.

The authors conclude that the prevalent concept of virus excretion of poliomyelitis is incorrect when it assumes that for only four weeks is the virus excreted in the stool of a patient with poliomyelitis. Their data show that this excretion extended into the eighth week in an appreciable percentage of cases. However, there was no evidence for the existence of a persisting carrier state for poliomyelitis.

Casey<sup>137</sup> gives an epidemiologic report on the most severe epidemic of

infantile paralysis on record in the state of Alabama. One hundred and twenty-one cases in one county were officially reported during the epidemic. There was evidence of patient-to-patient contact in 80 per cent of the cases in which an adequate history was obtained. The contacts were almost entirely among children under fifteen years of age.

Poliomyelitis is a self-limited disease, according to Key.<sup>138</sup> If deformities are prevented, the end result is determined largely by the damage done to the motor cells during the acute febrile stage. Key stresses the fact that many patients recover without treatment. Conversely, other patients remain paralyzed despite adequate treatment. Dividing the disease into stages, the author feels that in the acute febrile stage medical care and protection from irritation is used. In the subacute stage, rest and immobilization are the cardinal features of treatment. Relief from pain and protection of paralyzed muscles from gravity effects are important. In the convalescent stage, the patient must be trained to use his weak extremities. In the chronic stage, we must prevent the late deformities and aid function by braces and surgery.

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## THE RESPIRATORY TRACT

CHARLETTA K. WEYLAND, M.D.

### Generalized Obstructive Emphysema in Infants

The importance of generalized obstructive emphysema as a manifestation of a variety of acute and chronic respiratory disturbances of infants is emphasized by Nelson and Smith.<sup>139</sup> A state of generalized obstructive emphysema is produced whenever there is widespread partial blockage of the bronchioles resulting from any infections or mechanical causes. In such instances, because of the

mechanics of respiration, there is less restriction to the entrance of air in the alveoli. If the bronchial or bronchiolar obstruction becomes complete, absorption of the trapped air results in atelectasis, and areas of emphysema are interspersed with areas of atelectasis of varying size. Secondary infection may and often is responsible for diffuse suppurative lesions. The rapid resolution of sulfonamide-treated pneumonia infection has resulted in apparent increase in re-

spiratory disturbances characterized by generalized obstructive emphysema, many of which do not respond to sulfonamide or antibiotic medication. Among the various conditions which have been observed to be responsible for widespread bronchiolar obstruction with secondary emphysema, are acute bronchiolitis or interstitial pneumonia (probably viral in origin), atypical forms of acute tracheo-bronchitis, aspiration of large amounts of amniotic fluid and its contents during or just prior to delivery, aspiration of zinc stearate powder, respiratory infections associated with cystic fibrosis of the pancreas, and chronic passive congestion secondary to a congenital cardiac lesion.

Clinically, there is an expiratory type of dyspnea. While the respiratory rate is markedly increased, there is a distinct decrease in the respiratory excursion because of the overdistended lungs which cannot be emptied through the narrowed bronchioles. In an effort to compensate, the accessory muscles of respiration are brought into play and there is indrawing at the suprasternal notch and at the lower end of the sternum. This indrawing, however, is quite slight in comparison with that associated with laryngeal obstruction in which the difficulty in respiration is principally inspiratory and the lungs are being progressively deflated in contrast to the increasing inflation of expiratory dyspnea. In the more severe cases there is cyanosis. The percussion note is hyperresonant except over extensive localized area of consolidation, and the respiratory murmur is characterized by a prolongation and usually a roughening of the expiratory phase. There may or may not be fine or medium râles. The roentgenographic and fluoroscopic examinations of the chest are of the greatest help in diagnosis. The leaves of the diaphragm are markedly depressed and flattened, and

in place of the usual wide "doming" excursion there is, in the severe cases, only a quivering movement. The ribs are more widely separated than usual, the lung fields, less dense, and there may or may not be stringy or patchy dense areas or larger atelectatic areas.

Treatment of these conditions was not discussed since it varies to some extent with the underlying cause. In general, however, these are indications for the administration of *oxygen* (interspersed at intervals with O<sub>2</sub> and CO<sub>2</sub> to avoid the drying effect of oxygen alone) and the use of a *sulfonamide* or *penicillin* for secondary bacterial infections. Whenever there is blockage by secretions in the larger air passages, bronchial aspiration is indicated.

### Staphylococcic Pneumonia

Preliminary reports in the literature indicate that *penicillin* is more effective than the *sulfonamides* in the treatment of staphylococcic pneumonia in infants. McBryde<sup>140</sup> cites two cases in which sulfadiazine in adequate dosage had been tried without effect and was discontinued in favor of penicillin. The infants, aged four weeks and five weeks respectively, were given initially 5000 units of penicillin, followed by 1000 units every two hours for three days. Improvement was noted in twenty-four hours and all infants were out of danger in three days. Phillips and Kramer<sup>141</sup> used somewhat larger doses of penicillin in the treatment of five cases of *Staphylococcus aureus* infection of the lungs in infants less than three months of age. The initial dose in these cases was 50,000 units, with total doses ranging between 70,000 units and 640,000 units given over periods of seven to twenty-eight days. The antibiotic therapy was supplemented by oxygen, parenteral fluids, and blood transfusions and by operative

procedures as they were indicated in the cases of suppurative lung disease. As further supportive therapy, McBryde stresses the importance of alleviating the nasal obstruction which accompanies respiratory tract infection in young infants. The increased respiratory effort

repeated nasal suction, and continuous administration of oxygen.

**Prevention of Pneumonia During Upper Respiratory Infections in Infants**—Based on experimental work in the production of respiratory infection, Adams<sup>1+2</sup> suggests that posture may be



Fig. 8—A planogram (body section roentgenogram) of the lung, showing the slope of the trachea and main bronchi with respect to the ventral surface of the body. (Adams, J. M.: *J. Pediat.* 25: 369 (Nov.) 1944.)

occasioned by the material obstructing the nasal passages tends to cause the infectious material to be spread from the upper respiratory tract down into the bronchial tree and the alveoli. He suggests the irrigation of the nasal passages with 0.25 per cent neosynephrine hydrochloride or some other shrinking agent,

a factor in the prevention of acute pulmonary infection. The backward slope of the trachea and bronchi appears to be an important anatomic factor in the transport of infection from the upper air passages to the lungs. When the infant is placed flat on his abdomen, the angle which the trachea and the main bronchi

makes with the ventral surface of the body is about  $20^{\circ}$ . If the infant is placed in a prone position and is allowed to draw up his knees, there is a downward slope of the trachea from the corina to the pharynx, so that the lung fields are drained of secretion, and the material in the upper respiratory tract tends to flow by gravity out of the nose and mouth instead of into the lower respiratory tract as it would if the position were reversed.

**Sulfonamide Prophylaxis of Respiratory Infections**—A number of articles have appeared in the last few years relative to the use of sulfonamide drugs as prophylactic agents against respiratory infections. Siegel<sup>143</sup> observed 128 physically normal children ranging in age from two years to four-

teen years. Half of them received sulfadiazine daily in doses of 0.5 to 2 gm.; the other half were untreated and served as controls. The incidence of acute respiratory infections was approximately the same for the treated and the control groups, but those in the treated group recovered somewhat more promptly than those in the control group. It was pointed out that successful chemoprophylaxis requires the existence of specifically susceptible persons exposed to virulent bacteria which can be controlled by the action of the employed drug. Under other circumstances than this, the advantage may be slight, and in some cases the drug may be decidedly dangerous. This type of prophylaxis is not advised as a general measure.

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## TUBERCULOSIS

WALDO E. NELSON, M.D.

**Treatment of Primary Infection—Restriction of Activity**—In view of the wide divergence of opinion concerning the benefit of restriction of activity during the active phase of primary tuberculous lesions, the report of Levine<sup>144</sup> is of particular interest.

Among a group of tuberculous contacts, ninety infants were observed before, during, and after their primary tuberculous involvement. Twenty-seven of these infants had a primary pulmonary lesion before they were twelve months of age. These infants were classified as non-ambulatory. Of the twenty-seven infants, sixteen died and one developed tuberculosis of the hip.

Of the remaining sixty-three infants, sixty of them were ambulatory throughout the course of the primary tuberculous infection, irrespective of the extent of the pulmonary infiltration. Of the

sixty ambulatory patients, only four died from tuberculosis and two others developed disseminated lesions. Three of the infants were hospitalized; of these, one died from tuberculosis and one developed tuberculosis of the spine.

There was no evidence that rest in bed influenced the course of the primary tuberculous lesion or reduced the incidence of complications, and no evidence that lack of rest in bed was in any way detrimental. The average time from parenchymal infiltration to earliest signs of calcification of the primary focus was seven plus months, and to complete calcification, twenty-one plus months.

From these observations, it would appear that the age of the child at the time of infection rather than the method of treatment was the important factor in determining prognosis. Data were also assembled which indicated that contact

with a tuberculous mother during the first year of an infant's life was much more dangerous than contact with a tuberculous father.

The author concluded that *rest* in bed during a primary tuberculous infection should be limited to the period of elevation of temperature, as would be advised in the treatment of any febrile condition during childhood.

**Prevention of Tuberculosis**—Further evidence that *BCG* can be administered to humans with safety and possibly with some increase of immunity to tuberculous infection is contained in the report of Rosenthal, Bland, and Leslie.<sup>145</sup>

It was found that *BCG*, employed as a prophylactic agent, was innocuous in animals studied over a period of ten years, and in infants studied over a period of seven years. In 1204 vaccinated children, where no source of contact with tuberculosis was known, there were only 3 cases of tuberculosis and 1 death from the disease; in 1213 controls, there were 23 cases of tuberculosis and 4 deaths from the disease. In ninety-eight vaccinated newborn infants who were in contact with tuberculosis following vaccination, there was one case of tuberculosis and no deaths. If the contact and noncontact groups were considered

as a whole, there were twenty-seven cases of tuberculosis in the control group as against only four cases in the vaccinated group; there were seven deaths in the control group and one in the vaccinated.

**Nontuberculous Pulmonary Calcifications**—Recent observations by Palmer<sup>146</sup> apparently provide an explanation for some of the nontuberculous pulmonary calcifications which in recent years have aroused interest concerning their etiology. In certain sections of the country (principally midwest and midsouth), he has found a high increase of positive skin reactions to histoplasmin, a tuberculinlike compound obtained from the cultural products of *Histoplasma capsulatum*. The test groups consisted of student nurses. In a large series of cases, there was a positive correlation between the incidence of positive skin reactions and the presence of nontuberculous calcified lesions (negative tuberculin reactors). It has generally been considered that histoplasmosis is a rare, highly fatal infection. These data, however, suggest that, similar to tuberculosis and coccidioidomycosis, it may be a widespread (in certain geographic regions) mild infection and infrequently a serious disease in man.

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## SMALLPOX

ROBERT A. LYON, M.D.

An epidemic of severe smallpox occurring in the British Armed Forces recently in Egypt has been described by Illingworth and Oliver.<sup>147</sup> The course and characteristics of the disease in 100 consecutive patients served as a sample of the general epidemic. All forms of the disease occurred, but there was an unusually high incidence of the severe,

hemorrhagic types. Death occurred in 14 instances. The differentiation of smallpox from chickenpox and occasionally from measles and scarlet fever in the early stages was not easy. Such classical differences as the severity of prodromal symptoms, the nature and distribution of the eruption, the presence or absence of vaccination scars did

not prove effective in many cases. The presence of Paschen's inclusion bodies in the scrapings of smallpox lesions was of great assistance in establishing the diagnosis. All but 4 of the group of 100 patients had been vaccinated. Among the civilian population vaccinated by a three-scratch method, the severe hemorrhagic forms of the disease were less common than among the Army group vaccinated with the same lymph but by a single-scratch method.

Penicillin gave favorable results in the treatment of four patients with smallpox observed by Jeans, Jeffrey, and Gunders.<sup>148</sup> In a small but severe epidemic occurring in Italy, the four patients had progressed to the pustular stages of the disease and the lesions contained *Staphylococcus aureus*. All of the group had had *sulfathiazole* from the onset of the illness but, when *penicillin* was administered in average amounts of 400,000 units beginning on the sixth day after onset of the disease, rapid improvement occurred in three patients, and one died. Although the drug probably had no effect on the virus of the disease, it seemed to aid considerably in overcoming the secondary infection.

**Vaccination**—Some reasons for the failure of vaccination to protect individuals from smallpox have been discussed by Stevenson.<sup>149</sup> It is possible, in the first place, for vaccine lymph to be less potent than is required to produce protection in the patient. Generally, however, the poor results can be attributed to the variation in the patients' response to vaccination so that there is inadequate protection even when extensive or numerous areas have been inoculated. It must be remembered that only the failures have been reported in the literature, while the fact that the procedure is suc-

cessful in the great majority of cases is sometimes overlooked.

Diffuse glomerulonephritis occurred as a complication of vaccination in a patient sixty-seven years of age, observed by Herbut.<sup>150</sup> The patient had had a successful vaccination "take" thirty years previously but on revaccination had a severe take and generalized macular eruption. The kidney involvement probably started about one week after vaccination and death occurred thirty-seven days after the vaccination. The urinary findings and the pathological examination demonstrated an acute glomerulonephritis.

A fatal case of vaccinia in an infant with eczema has been reported by Peter-silge and Toomey.<sup>151</sup> The infant, who was eight months old, contracted the disease from a sibling who had been vaccinated. A confluent pustular eruption developed on the face, palpebral conjunctivae, knees, and wrists. He died fourteen days after the onset of the eruption.

*Generalized vaccinia*, which occurred in a child with eczema, has also been described by Hershey and Smith.<sup>152</sup> The child, one year of age, was exposed to the vaccination "take" of her brother and soon developed extensive lesions on the face, arms, and back. The vaccinal virus was demonstrated in the lesions and its protective antibodies were demonstrated in the patient's serum after recovery. The author found that the incidence of vaccinia had varied from 1 in 20,000 to 1 in 96,000 vaccinations in different surveys. The case fatality rate has varied from 12 to 30 per cent. It seems probable that the virus may be inoculated into eczematous lesions by direct contact with a "take," or it may be spread by droplet infection from the vaccinated person. Vaccine virus has been found in the nasopharynx of vac-



nated persons on the fourth and fifth days after vaccination and it has also been recovered from the urine. The treatment of patients with vaccinal lesions of this sort has consisted chiefly of *transfusion of blood* from patients who have recently recovered from vaccination. Local applications of *potassium permanganate* solution have been effective in killing the virus. In many instances there apparently is secondary infection with streptococci and other pyogenic organisms so that treatment with *sulfonamides* and similar chemotherapeutic agents should be given a trial. Occasionally, a herpes virus has been isolated from the eczematous vaccinal lesions but often neither herpes nor

vaccinal virus has been obtained. It seems possible therefore that any one of several viruses may invade eczematous lesions to produce serious complications.

*Convalescent serum* seemed to hasten the recovery of a patient with generalized vaccinia reported by Chesney and Jubb.<sup>153</sup> The eruption began about ten days after the vaccination and the child developed high fever, lethargy, and severe toxemia. Some of the symptoms were suggestive of encephalitis. Following the injection of 20 cc. of serum obtained from a patient who had recently recovered from a successful vaccination, the child's symptoms subsided and the eruption began to fade.

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## SYPHILIS

RICHARD E. WOLF, M.D.

In a brief preliminary note, Platou *et al.*<sup>154</sup> summarize their experience in the treatment of sixty-nine infants with manifest early congenital syphilis treated with *sodium penicillin*. Penicillin was administered intramuscularly in saline solution every three hours in sixty injections over a seven and one-half-day period. The total dosage used ranged from 16,000 to 32,000 Oxford units per kilogram of body weight.

In thirty-four of these sixty-nine infants, there were reactions during treatment. However, nearly all of these reactions were mild and consisted of moderate fever seldom lasting more than three days. One infant, forty-eight hours after treatment was begun, suddenly developed severe, nearly fatal collapse. There were five deaths in the series. Three infants died during or soon after treatment. All of these were infants

under two months of age and in poor general condition.

In general, the results were gratifying. All dark-field positive lesions became negative within twenty-four hours after starting penicillin therapy. X-ray evidence of syphilis disappeared in two to six months.

Thirty-nine of the infants were followed for four to twelve months. Of these, twenty-five were physically normal and showed negative or doubtful serologic tests. Nine others had moderately high quantitative serologic titers which were either stationary or declining slowly.

Serologic relapse occurred in five infants and clinical relapse in two of these five. Serologic relapse occurred from three to six months after treatment, and clinical relapse in each case at six months.

Lentz, Ingraham, Beerman, and Stokes<sup>155</sup> report the results of the treat-

ment of nine infants with congenital syphilis with penicillin. Of these, two infants died. Only three of the remaining patients were followed long enough to make a report on their progress. All three infants had relatively high blood serologic titers initially, but these dropped sharply during the period of observation. Two infants who showed roentgenographic evidence of osteochondritis and periostitis have resumed normal bone development.

The dosage employed varied between 16,000 and 19,000 units of *sodium penicillin* per pound of body weight. This was given intramuscularly in divided doses every four hours over an eight-day period.

The only definite treatment reaction noted among the seven infants who are still living occurred during the first forty-eight hours. The infant had received 19,000 units of sodium penicillin and then developed severe dyspnea and cyanosis which necessitated the administration of *oxygen*. His condition remained critical during the next twenty-

four hours during which penicillin was withheld. The drug was then resumed in full dosage without further difficulty, and with a favorable outcome. This was the only infant who developed a completely negative blood serologic reaction. The authors felt that it was highly possible that this severe reaction was a Herxheimer reaction.

It was difficult to evaluate the two deaths inasmuch as there was another cause of death in each case. In one case, a possible congenital heart lesion and, in the other, a severe diarrhea with dehydration caused the death. It may be significant that each of the infants in whom severe reaction or death occurred was less than two months of age. The author stresses the fact that the real danger of too energetic arsenotherapy also lies in these first few weeks of life when the infection is overwhelming and the infant's resistance undeveloped. The treatment of such young infants with congenital syphilis should be approached with extreme caution and reduced dosage of penicillin.

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## TETANUS

NINA A. ANDERSON, M.D.

Buxton and Kurman<sup>156</sup> have treated two patients with tetanus, one of them a child, with *penicillin* in addition to tetanus *antitoxin*. They believe that the addition of the penicillin in the treatment of each of these instances was a lifesaving measure. Tetanus antitoxin was administered intramuscularly and intravenously, penicillin intramuscularly, and *dihydromorphinone hydrochloride*, *seconal sodium*, *sodium bromide*, and *chloral hydrate* were given for sedation as necessary.

Cole<sup>157</sup> reports an instance of severe local tetanus which developed during the course of a mild generalized attack in a five and one-half-year-old boy who had injured his left foot when he trod on a rusty nail and developed symptoms of tetanus three days later. Signs of local tetanus were very slight when the signs of generalized tetanus were marked; after antitoxin had been given, marked stiffness and rigidity of the left leg developed and persisted throughout the whole illness and even longer than signs

of tetanus in other parts of the body. In another instance of tetanus, in an eight-year-old boy, this author obtained control of reflex convulsions and promoted sleep with intramuscular paraldehyde in doses of 2 or 3 cc. given twice every twenty-four hours for the first few days and later once daily. A plaster-of-paris bandage kept the needle of an intravenous drip in the vein during the period when convulsions were frequent and severe. A threatening pulmonary infection was abated by the administration of *sulfathiazole*.

**Immunization**—There is a growing interest in the use of combined immunization procedures, for which there are obvious advantages if they provide adequate prophylaxis against disease. Hamilton and Knouf<sup>158</sup> have used a mixture of fluid toxoids of diphtheria and tetanus and added phase I pertussis vaccine, the fluid concentration yielding the usual dose of the two toxoids plus 40,000 million pertussis organisms per cubic centimeter. The children who were immunized with this material ranged between one and two years in age, most of them between twelve and fifteen months, and they received 0.5-cc., 1-cc., and 1-cc. doses subcutaneously in the deltoid region at about four-week intervals. There were no significant reactions from these injections; in a few instances, the infants were irritable and seemed to have a little tenderness at the site of the injection but no nodules were found. When the two toxoids were adsorbed on aluminum hydroxide, however, and used for another group of patients, painless nodules developed rather frequently. The results with the mixed antigen showed laboratory evidence of immunity which compared favorably with those expected when each antigen was given separately. A few infants have been exposed to whooping cough without contracting the

disease, but the total number is too small to be of significance.

An adequate tetanus antitoxin titer was obtained on the seventh day after the injection of the third or "booster" dose of 0.5 cc. of *tetanus alum-precipitated toxoid*, in each of twenty-five allergic children, all of whom had attained adequate immunity after receiving the two initial doses of the combined diphtheria and tetanus alum-precipitated toxoids four years before. Peshkin<sup>159</sup> found the maximum titer one month later in the majority of the instances; it was maintained at an adequate level one year later. This titer was higher and lasted longer than that which followed the basic or initial immunization as well as that which followed administration of a "booster" dose of toxoid three to fifteen months after immunization. The titer, however, was comparable to the maximum titer response following a "booster" dose of toxoid given two years after basic immunization. The titer was not as high as that obtained in those instances in which the "booster" dose was given three years after basic immunization. No febrile nor systemic allergic reactions occurred. Scratch tests with the undiluted combined toxoid and with tetanus toxoid alone did not produce positive reactions in any of the children, before the "booster" dose or from one to six months thereafter. The author uses alum-precipitated tetanus toxoid alone for the third injection in order to keep local and systemic allergic reactions at a minimum level.

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## RADIOLOGY

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### ROENTGEN THERAPY

ROBERT P. BARDEN, M.D.

#### Acute Encephalitis

Although virus encephalitis occurs in various forms with differences in the clinical picture and the prognosis, certain features are common to all types. This disease is a nonpurulent inflammation of the brain and its covering. In the acute stages are various degrees of hyperemia, hemorrhagic reaction, cellular infiltrations, especially of lymphocytes, and proliferation of glia cells. In later stages various degenerative changes develop in blood vessels, nerve tissues, and meninges. These late changes occur in scattered areas of the brain and its covering, resulting in a diversity of symptoms and signs. The differential diagnosis includes lymphocytic choriomeningitis, early disseminated encephalomyelitis, acute multiple sclerosis, spontaneous subarachnoid hemorrhage, subdural hematoma, brain tumor or abscess, atypical type of meningitis, and poliomyelitis.

Animal experiments have shown that encephalitis may be prevented or cured in the laboratory. Reports of beneficial results of roentgenotherapy in the human disease are becoming more numerous. The recommended method of treatment is to use factors suitable for any inflammatory process giving a total dose of 300 r. or less to each side of the head

and base of the skull. The earlier the radiation therapy is instituted, the better the results obtained. In a recent review of forty-nine cases, twenty-nine were found to have recovered dramatically following radiotherapy and fifteen were greatly improved, one patient died, and four were lost to follow-up. Reports such as the above are encouraging for the future management of virus encephalitis for which no specific treatment has yet been devised. It would also seem reasonable to investigate the possible therapeutic benefits of radiation therapy in poliomyelitis because of the similarity in the underlying pathology of these two conditions. If experience shows that poliomyelitis can be controlled in a way analogous to the reports on encephalitis, a valuable contribution to preventive medicine will have been made.<sup>1</sup>

#### Carcinoma of the Mouth

Statistical studies indicate that 7 per cent of all fatal cancers in man originate in the oral region. Regardless of the location of the tumor, it is useful to classify it as to clinical type with stage I representing very small lesions, stage II representing large local lesions without extension, stage III representing lesions with local extension, and stage

IV representing those with metastases to regional lymph nodes. The discouraging feature of the report from most clinics is that regional lymph node metastases are present in approximately 50 per cent of the patients when they first appear for treatment. These lesions are practically all squamous cell in origin. The average duration of symptoms before the institution of treatment is between eight and nine months, and usually the patients do not present themselves until pain or swelling occurs. The small indurated ulcerating lesions are the more malignant while the papillary lesions developing upon an area of leukoplakia are often relatively benign. The general principles of treatment may be considered under three headings: (1) Hygienic care of the oral cavity before, during, and after treatment; (2) treatment of the primary lesion; (3) management of cervical metastases. Preliminary cleaning up of the mouth includes removal of all broken, jagged, infected teeth as well as all teeth in the proposed field of irradiation. Daily mouth washes or saline irrigation is advised. Necessary vitamin therapy should be prescribed, and the use of tobacco discouraged. In the treatment of the primary lesion, irradiation will usually be the method of choice. It is well to remember that it will take 7,000 to 10,000 gamma-ray roentgens delivered in ten to twenty days to destroy epidermoid carcinoma. The usual plan of treatment is to apply a radium mold followed by external irradiation over a period of twenty-one to twenty-eight days. Gold radon implants are then inserted into soft tissue lesions and around metastatic nodes. If any persistence is noted two months later, a radical resection is advised in operable cases. The external radiation is given with a 200-KV unit with 0.5 to 1.0 mm. of copper filtration at a distance of

50 to 60 cm. Multiple fields are treated, usually three, sometimes four, giving 200 to 300 roentgens in air to one field each day, to a total of 3000 roentgens. The radium doses should deliver from 4000 to 7000 gamma roentgens to the lesion. In the consideration of the treatment for metastases, it is well to remember that bilateral metastatic lymph nodes are not uncommon.

The control of the primary lesion is the first requisite in treatment of the metastatic node. If this can be controlled and no lymph nodes are palpable, the question of prophylactic neck dissection has to be decided. Most authorities agree that neck dissection should not be undertaken until palpable nodes are present. This means that careful and frequent examination of the lymph drainage areas has to be undertaken in all patients so that surgery of the neck may be used with the very first appearance of lymph node enlargement. When isolated lymph nodes are found, they may be removed surgically or treated by implantation with radium needles. External radiation is a useful adjunct but cannot be relied upon to sterilize metastatic lymph nodes when used alone. Complications following irradiation include hemorrhage, local soft tissue necrosis, and radiation necrosis of bone, which occurs in a high proportion of patients with alveolar ridge lesions. The following are among the best overall cure rates reported for carcinoma of various locations in the mouth: upper alveolar process, 47 per cent five-year cures; lower alveolar process, 38 per cent five-year cures; cheek, 18 per cent five-year cures; floor of the mouth, 10 to 20 per cent five-year cures; hard palate, 20 per cent five-year cures.

Better results may be expected in the future in the treatment of the primary lesions by the increased use of intraoral therapy and possibly by the use of higher

voltages, and in the treatment of cervical metastases by more localized and intense irradiation.<sup>2</sup>

### The Treatment of Early Carcinoma of the Cervix

It is now generally accepted that the results of adequate radiation therapy are superior to those of the radical Wertheim hysterectomy in the treatment of epidermoid carcinoma of the cervix in all stages. On the other hand, the records of the best radiotherapy clinics show that 20 per cent of patients with stage I and 30 per cent of those with stage II carcinoma are not cured by even the most competent and skilful radiation therapy. It is logical to inquire whether radical surgery in these cases might not have saved some patients who were lost under radiation therapy. It is believed that this question cannot be answered by statistical analyses but only by an analysis of the individual failures. This is the responsibility of every radiation therapist dealing with cervical cancer in order that clear-cut indications for surgery may be evolved. Interest in this problem has been recently revived by eminent gynecologists such as Taussig and Meigs. It is recognized that a certain number of deaths following radiation in patients with early carcinoma are due to severe damage to the small intestines. However, it is by no means certain that such damage should occur if radiation therapy is properly administered. Two of the common errors in technic resulting in intestinal damage are the administration of the intracervical radium in large doses over a short period of time and improper direction of the beam of external radiation so that crossfiring occurs within the pelvis. It is suggested that a total dose of 8000 mg. hours of radium over a period of ten days is the optimum method

of treating the local lesion and that the external radiation be delivered through four portals directed at right angles to the transverse plane of the pelvis to the limits of skin tolerance. On the other hand, it must be admitted that even with the optimum radiation therapy there are patients with metastases to the lymph nodes which cannot be sterilized so that surgery theoretically would offer a better chance of cure. Since it is impossible to recognize these cases prior to treatment, it is most likely that from a statistical point of view the actual survival rate of patients with stage I and stage II carcinoma would be smaller if radical surgery were performed on the group as a whole than if radiation therapy were instituted. It is probable that if the radiation therapist and the gynecologist will carefully analyze the causes of failure in their own clinics in patients with early cervical carcinoma, they will be forced to admit that improvement of radiation therapy by more careful attention to details of technic and by the elimination of inadequate procedures of the past and careful adaptation of the individual procedure to the individual requirement of the patient will probably save more patients than a wholesale return to radical surgery.<sup>3</sup>

### Ovarian Tumor

Carcinoma of the ovaries is one of the most fatal of pelvic neoplasms, and treatment has always presented difficult problems. Surgery alone results in a low cure rate, and most observers agree that considerable improvement of this cure rate can be expected by the addition of postoperative irradiation. In the usual case the operation should remove all visible neoplastic tissues together with the pelvic organs. Postoperative irradiation has resulted in an increased cure rate of moderate degree in stage I; but in the



stage II, III, and IV cases, postoperative irradiation is imperative and has resulted in a considerable salvage. In some instances, the patient is thought to have an inoperable tumor when first seen; and in this situation irradiation should be given, although it is much safer to attempt to obtain a histologic diagnosis beforehand, either from examination of the cells in the ascitic fluid or by laparotomy and biopsy of the pelvic tumor. In some cases, a tumor originally inoperable becomes operable following irradiation and may be removed six to eight weeks after the end of the treatment. Under these circumstances, a favorable clinical sign is the decrease in the amount of ascitic fluid during the course of roentgen therapy.

The technical factors employed consist of high voltage, heavily filtered, long distance radiation. It is customary to treat through two anterior and two posterior portals including the lower half of the abdomen and pelvis with the total dose

per port in air roentgens of 2000 to 2500 r. over a period which averages about four weeks.

In a group of ninety-five patients with malignant ovarian neoplasm, the five-year survival rate following the above methods of treatment was 40 per cent. As in all recent statistics, the need of early recognition of ovarian carcinoma is stressed since this will result in a greatly increased rate of survival. Whenever surgery is attempted, it should result in the removal of as great amount of tumor tissue as possible, irrespective of how extensive the tumor is found to be, because the smaller the mass of tumor tissue left the better the result of post-operative roentgen therapy will be.<sup>4</sup>

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## ROENTGEN DIAGNOSIS

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### Close-Range Roentgenology

Although well-established principles of roentgen technic prescribe the use of a target film distance of 30 inches or longer, there are certain anatomical structures, particularly the surfaces of bone, which may be clearly demonstrated free of the surrounding shadows by adopting a technic which calls for a much closer target film distance. With the tube 15 inches or less from the film, objects which are resting against the film or are less than 2 inches away from it will be very little distorted; but blurring and distortion of the images of objects at a greater distance than 2 inches

from the film increases greatly. The technic consists in very accurate localization of the area to be studied, and the use of a focal spot film distance of 10 to 15 inches with a very small short cone. Fine grain film or no-screen film may be used to advantage without prolonging the exposure time more than one would have to use at the standard distance. Although the image of the object appears enlarged, this may at times prove helpful in the more detailed study of a structure. It has proved particularly useful in examinations of the temporomandibular joint, the sternum, the inner end of the clavicle, fracture of the skull,

demonstration of sequestra in osteomyelitis, osteochondritis dissecans, meningioma, and many other conditions where a finer analysis of a circumscribed area of bone destruction is required.<sup>1</sup>

### **Intracranial Angiography**

Radiographic examination of the skull following the perfusion of intracranial vessels with radiopaque material has been increasingly useful since the procedure was first applied by Moniz in 1927. Blood vessels momentarily rendered densely opaque serve as reference points in detecting disturbances of anatomical relationship produced by intracranial lesions. This method is very useful when vascular displacement provides evidence of disease in neighboring tissues and is of special value when the vessels are involved directly. In particular, the procedure offers a means of obtaining diagnostic information, not otherwise available, in suspected intracranial aneurysms, anomalies of intracranial vessels, certain cases of arterial occlusion, and expanding lesions involving one cerebral hemisphere which have not been accurately localized. Sometimes the vascular pattern provides an indication of the character of the pathological process, the best example of which is the appearance seen in deeply placed hemangiomas. When supratentorial structures are to be examined, the internal carotid artery is the site of injection; whereas angiographic exploration of the posterior fossa necessitates injection of the vertebral system.

Normally, it requires about four seconds for blood to pass from the carotid artery by way of the various cerebral vessels to the large intracranial sinuses. By proper timing of injection and roentgen exposure, either the arterial or the venous phase of the cerebral circulation can be recorded. In order to obtain

maximum contrast within the injected vessel, the opaque material must be injected as rapidly as possible. The technic consists in surgical exposure of the internal or common carotid artery with the use of local anesthesia. Thorotrast is injected through an 18-gauge needle connected to a syringe by a 10-cc. length of pliable, noncollapsible tubing. Ordinarily, three injections should be made: two to obtain stereoscopic lateral views, and a third for a single anteroposterior projection. If each injection is limited to 10 cc., the total of 30 cc. of thorotrast will not produce any harmful effects after it is stored in the reticuloendothelial system. A suggested method of performing the injection is as follows: When the opaque material is two thirds injected into the vessel, a signal is given for the first roentgen exposure. As soon as the films can be changed, usually about three seconds later, a second exposure is made. This is intended to record the venous return. Without disturbing the needle and tubing, the empty syringe is replaced by one containing Ringer's solution and the rubber tubing and needle are flushed to prevent clotting. The radiographic tube is then shifted for stereoscopy and a second injection is performed in an identical manner. The film of the third injection is made in the anteroposterior plane with the central roentgen beam passing through a plane of the skull which includes the external auditory meatus and a point in the midline of the forehead 5 cm. above the glabella.

Contraindications to cerebral angiography are the presence of hypertension, far-advanced arteriosclerosis, acute intracerebral or subarachnoid hemorrhage, recent thrombosis, or embolism of the cerebral vessel. Injection of the carotid is technically much more simple than injection of the vertebral artery, and is,

therefore, more widely practiced; but it is obvious that with carotid injection no information will be obtained about lesions in the posterior fossa and also that preliminary lateralization of the lesion must have been accomplished before the injection is proposed.<sup>2,3</sup>

### **Response of the Retina to the Direct Roentgen Beam**

In many instances of injury to the eye, ophthalmoscopic observation is impossible because of severe edema of the lids and conjunctiva or cloudy media. In these patients, accurate information concerning the condition of the retina may be obtained by exposing the injured eye to the direct roentgen beam. The principle employed is dependent upon the recognition of a diffused bluish-green glow by the intact retina after the patient has become completely dark-adapted. The actual technic consists of placing the patient in a darkened room for twenty minutes preceding the examination. During this interval, the procedure to be undertaken is carefully explained. The subject is positioned facing the x-ray tube so that the field irradiated may be noted on the fluoroscopic screen. The examiner then ascertains the ability of the patient to recognize the retinal response to the roentgen beam with the uninjured eye. To assure comprehension and complete cooperation, the patient is required to describe accurately the effects of irregular and repeated interruptions of the current. When accuracy of observation with the uninjured eye is demonstrated, the beam is shifted to the injured side. If the patient appreciates a homogeneous glow with direct radiation, an intact retina may be assumed to be present. Absence of response may indicate either retinal detachment or a lesion involving the visual pathway. A darkened area in an otherwise homo-

geneous field usually can be mapped by the patient in the presence of partial detachment, perforation, or tear of the retina. The condition of the globe anterior to the retina does not alter this response since hemorrhage into or clouding of the media due to other causes does not affect appreciably the roentgen beam. With clear media and an intact retina, radiopaque foreign bodies anterior to the retina appear to sparkle when observed by the patient in the direct beam. If this sensation is appreciated by the patient, he can localize the particle fairly accurately in the visual field. Occasionally, nonradiopaque foreign bodies may be identified by the patient during this procedure. Since x-rays are not refracted by the crystalline lens in the eye as is ordinary light, the area of the retinal defect or the image of the foreign body is reversed only in the higher centers, and therefore is diametrically opposite that described. Thus, if a patient describes a scintillating spot in the right eye at two o'clock, its actual location would be at eight o'clock. The same holds for retinal tears. The use of this method of assessing the integrity of the retina should be of great value in determining whether immediate surgery or more conservative measures to save vision should be employed.<sup>4</sup>

### **Ossification of the Choroid Layer of the Eye**

Four groups of intraocular calcium shadows may be mentioned: Calcification of the lens, ossification of the vitreous, calcified carotid or ophthalmic arteries, a shrunken calcified globe. Shadows produced by intraocular calcium can be readily distinguished from those due to metallic foreign bodies, to iron impregnation following incomplete removal of metallic dust, and to residual thorotrast following orbitography. The

ossification is thought to be subsequent to a degeneration of the lens fibers, no matter what the etiology of the preceding cataract may have been. Long-standing, severe uveitis, and subsequent disorganization of the eye, favor deposits of bony tissue on the inner side of the choroid starting usually near the entrance of the optic nerve and extending toward the ciliary bodies, often forming



Fig. 1.—Twenty-one-year-old colored male with history of cerebral meningitis eight years previously. Chorioretinitis developed, followed by blindness of both eyes; note the distinct annular calcium shadows within the orbits. (F. G. Kautz and I. Schwartz: *Radiology* 43: 486 (Nov.) 1944.

an almost complete osseous cup. This type of ossification usually follows a serious long-standing inflammatory condition which in many instances was primarily caused by direct penetrating injury or by repeated infection. The differential diagnosis, from a clinical standpoint, may often include glaucoma, sympathetic panophthalmia, or tumor. The diagnosis is definitely established by the roentgen finding of rather typical shadows of bony density in the globe. Usually there is a shrunken eyeball, a large central area of which is occupied by a well-delineated, fairly regular ovoid

circular or semicircular calcium shadow. This shadow often occupies the region of the lens and extends more frequently into the posterior portion of the eye. If the lens is luxated, the shadow shifts accordingly. Occasionally, the shadow may assume the shape of a ring a few millimeters in thickness. Metallic foreign bodies may be observed near the calcification. The roentgenographic image corresponds to this finding of shell-like ossification of the choroid and of the lens. There may be additional small calcium densities scattered throughout the eyeball according to the extent of the choroid involvement and invasion of the cornea. This condition occurs in adults which serves to distinguish it from the calcification occasionally seen in young children with retinoblastoma. The differential roentgen diagnosis includes foreign bodies, vascular calcifications, phleboliths, orbital angioma, osteoma, and endocranial calcification; but none of these conditions provides shadows which could be confused with a calcified choroid. It is important in obtaining roentgenograms to be sure that the eye is not moved during the roentgenographic exposure. Inasmuch as these calcifications have been noted in patients where the lesion was unsuspected, it would seem useful to routinely warn the patient in whom sinus or skull films are being obtained not to move the eye during the exposure. The shadows are best seen on films made with the patient's head in the Water's position, by direct lateral views of the orbit, and by bone-free films in which a dental film is placed at the inner canthus of the eye and a tangential view of the anterior portion of the orbit obtained.<sup>5</sup> (Fig. 1.)

### Aerosinusitis

Among the problems peculiar to aviation medicine are otorhinological affec-

tions caused directly by the action of rapid changes of barometric pressure on aviators during flight and on personnel in altitude chambers. These changes are reflected more or less closely in the paranasal sinuses and in the middle ear which are connected to the nose and nasopharynx by relatively narrow passageways. Blockage of these ostia results in unequal pressures and calls forth an inflammatory reaction in the sinus cavity. The symptoms of aerosinusitis and aero-otitis media are manifested generally by a sudden severe unremitting pain, boring in character, and localized over the region affected. The pain occurs abruptly during descent from regions of low atmospheric pressure and is probably due to the sudden stretching and separation of the mucoperiosteal tissues during the rapid swelling that follows plugging of the ostium. The soft tissue swelling can be easily demonstrated roentgenographically and may be due either to edema or hemorrhage. If bleeding has occurred, blood may remain in the sinus or middle ear for a considerable period of time, if patency of the ostium is difficult to reestablish. It is evident that the changes due to atmospheric pressure variations are more likely to occur in sinuses or middle ears which have been previously involved in infection.

Treatment consists in instituting *slow decompression* similar to that used in the treatment of "the bends" or caisson disease. The patient is placed in a chamber with low atmospheric pressure and slowly returned to normal atmospheric pressure. This may often be sufficient to overcome the severe pain. Thereafter, persistent and continuous shrinkage of the nasal mucosa or the pharyngeal mucosa is the only effective method of maintaining patency of the ostium. The neglected or incompletely treated cases

may be disabled for weeks. Total resolution is demonstrated by complete return to normal appearance of the sinus or mastoid on the roentgenogram. This occurs some time after the clinical subsidence of symptoms.<sup>6</sup>

### Calcification in Syphilitic Aortitis

The high correlation between the roentgen finding of calcification in the ascending aorta and the presence of syphilitic aortitis has not been sufficiently recognized. It would seem as if calcification localized to the ascending aorta has a different significance than that seen in the aortic arch or descending aorta and commonly ascribed to arteriosclerosis. Similarly, calcification seen in the walls of aneurysms is also of no help in determining the etiology. Even though no special methods are used to establish the presence of calcium in the ascending aorta, it will be seen in the routine chest film in 25 per cent of patients with known syphilitic aortitis. Bucky films would yield an even higher percentage. Usually the plaques can be distinguished in the ordinary postero-anterior projection, although occasionally oblique views are necessary to render them visible. It is suggested that the calcifications are usually found in longstanding cases of syphilis often when the serological evidence of the disease begins to disappear—the so-called burned-out stage. Because of the fact that luetic aortitis usually is present without any signs or symptoms and may be present without a positive Wassermann, the importance of the so-called "calcium sign" is evident. Careful study of a large number of patients with proven arteriosclerosis of severe degree indicates that calcium is rarely deposited in the ascending aorta in a mass which can be demonstrated roentgenographically. Identification of calcium in the primary

portions of the aorta thus becomes an extremely simple and practical method of suggesting the diagnosis of a condition which may otherwise remain latent for many years.<sup>7</sup>

### **Dissecting Aneurysm of the Aorta**

This condition is relatively uncommon, occurring in various statistics in about 0.4 per cent of autopsies. It is of clinical significance because it is usually confused with coronary disease, pulmonary embolism, or rupture of the heart. A dissecting aneurysm is produced by penetration of the circulating blood between the layers of the wall of the aorta as a result of a tear in the intima of the vessel and is usually associated with hypertension and arteriosclerosis. Rupture into the mediastinum, pleura, or the pericardium is common and usually results fatally.

In the acute cases there is usually sudden onset with severe pain in the chest or abdomen. The pain is apt to radiate rapidly as the dissection progresses. Collapse, shock, and death may occur immediately or after some delay.

The roentgen studies are of value in establishing the diagnosis and evaluating the progress of the disease. The significant roentgen findings are increase in the width of the shadow of the aorta, cardiac hypertrophy, pericardial effusion, and fluid in the pleural space. The finding of sudden widening of the shadow of the aorta, particularly if it is seen as a circular enlargement, should suggest the possibility of a dissecting aneurysm in a patient presenting the clinical findings given above.<sup>8</sup>

### **Congenital Absence of the Lung**

This condition is often found in conjunction with other developmental anomalies, and the most plausible explanation given is that it results from a defect in

the developing germ plasm which involves both the vascular and pulmonary structures on the affected side. The commonest finding is complete asymmetry of the lungs, although in a few instances cases of extreme hypoplasia of the lung or of a rudimentary lung bud about the main bronchus have been reported. The symptoms in the newborn may be entirely overlooked because they are often minimal in extent, but physical signs are those caused by the displacement of the mediastinum and heart toward the affected side. The opposite functioning lung is usually hypertrophied and over-ventilated. The differential diagnosis includes pneumonia, massive atelectasis due to obstruction of a main bronchus or diaphragmatic hernia, or eventration. The uniform dense shadow which covers the entire thorax should suggest the correct diagnosis, however. A final diagnosis is possible by the use of lipiodol bronchography which should be done through the medium of the bronchoscope. In the classical case there is complete obstruction in one of the main bronchi just below the bifurcation.

It is quite obvious that the prognosis in congenital absence of the lung should always be guarded. In the first place, there may be other unknown congenital anomalies which may of themselves prove serious. In addition, any otherwise insignificant involvement of the only existing lung may cause sudden fatality. However, several cases have been reported in the literature where patients have lived to extreme old age with this condition.

Interest in this rare congenital anomaly is heightened by the fact that a study of the embryologic development of the lung indicates a possibility of numerous less marked anomalies which may escape attention in an individual for long periods of time and yet be responsible for recur-

rent disease such as recurrent pneumonia or bronchiectasis. In cases of chronic or recurrent pulmonary diseases, congenital anomalies or obstructions in the tracheobronchial tree should be diligently sought, and this can only be accomplished by the more widespread use of lipiodol bronchography.<sup>9,10</sup> (Fig. 2.)

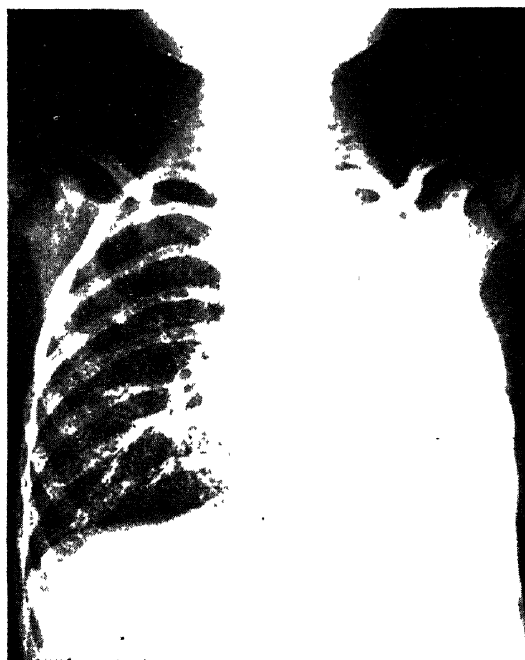


Fig. 2—Two-year-old white female with unproductive cough and noisy respirations. Patient still living six years after this roentgenogram was obtained. The illustration shows complete absence of left main stem bronchus, with lipiodol outlining the trachea and the right main bronchi, and considerable lipiodol is seen in the esophagus. (C. D. Ferguson and E. B. D. Newhauser: *Am. J. Roentgenol.* 52: 459 (Nov.) 1944.)

### Pneumomediastinum in the Newborn

The infant's lungs and mediastinum are particularly sensitive to changes in intrathoracic pressure, such as occurs during violent respiratory efforts in obstetrical labor, pertussis, and obstructive tracheobronchitis. Injudicious use of artificial respiration in the newborn is also responsible for abnormal intrathoracic pressures. Investigations in experimental animals indicate that when the

intra-alveolar pulmonary pressure is increased, rupture of the alveolar walls occurs, and air passes back toward the root of the lungs by means of the perivascular and perilymphatic areolar tissues. Mediastinal collection may quickly develop and often proceeds to unilateral or bilateral pneumothorax. Indeed, the development of pneumothorax may act as a decompression by removing some of the effective pressure upon the heart and great vessels and at the same time it may interrupt the passage of air through the abnormal pulmonary opening by compressing the affected lung. Again the air may work its way upward into the subcutaneous tissues of the neck or into the peritoneum. Mediastinal emphysema occurring during the first few days of life is usually manifested by respiratory distress. There are bowing of the precordium, distention of the neck veins, and a fall in the blood pressure. Auscultation of the chest may discover a peculiar crackling sound synchronous with a systolic cardiac contraction.

The diagnosis of this condition is essentially a roentgen procedure. All infants showing cyanosis and dyspnea soon after birth should be routinely examined by roentgenoscopic and P.A. and lateral views of the chest. In the frontal projections, air may be seen outlining the lateral margins of the superior mediastinum. In the lateral view, pneumomediastinum will show a large area of encapsulated air immediately posterior to the shadow of the sternum. The presence of a pneumothorax may interfere with or even obscure the shadows of the mediastinal air.

Treatment consists of the *control* of the source of *air* and the production of an *outlet* to the *air* already accumulated. In mild cases, conservative treatment with *oxygen* and stimulants has been sufficient; in the more severe cases,

*aspiration* of the air may be necessary and the possibility of a therapeutic *pneumothorax* to prevent reaccumulation of air should be considered.<sup>11</sup>

### Disseminated Calcified Nodules in the Lungs

The appearance of the roentgenogram of the lungs in long-standing cardiac disease may simulate hematogenous tuber-

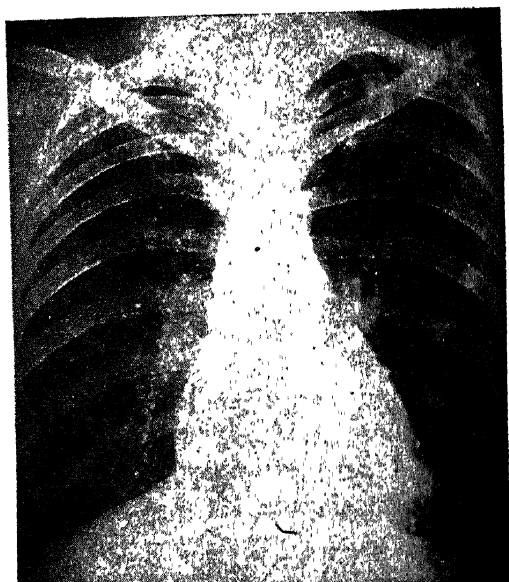


Fig. 3—Twenty-nine-year-old male with long-standing mitral stenosis. Died later of congestive heart failure. Note the widespread calcification with predominating distribution in the lower lung fields. (A. Grishman and I. J. Kane: *Am. J. Roentgenol.* 53: 575 (June) 1945.)

culosis, silicosis, or sarcoidosis. Indeed, in the literature mention of disseminated calcified or ossified nodular densities has only rarely been included in discussions of pulmonary findings associated with chronic heart disease. In most instances, these nodules are found in cases with long-standing mitral stenosis in whom cardiac failure has occurred one or more times in the past. The pathogenesis of the nodules is thought to be as follows: Plasma and red cells are present in the alveolar spaces as a result of congestion of the pulmonary veins and delayed re-

sorption results in organization of the transudate by connective tissue in which secondary calcification occurs. In some cases, however, it appears as if the development of the nodules were associated with the active phase of rheumatic fever. In the differential diagnosis, fungus disease, ascaris infestation of the lungs, and healed miliary tuberculosis, all have to be considered. The first two conditions have never been conclusively shown to produce calcified or ossified nodules and the presence of calcified miliary tubercles is exceedingly rare. The peculiar association of the nodulation with rheumatic mitral disease and the distribution of the nodules, mainly in the lower portion of the lung fields, are of prime importance in the correct interpretation.<sup>12</sup> (Fig. 3.)

### Calcifications in Silicosis

In recent years there have appeared occasional reports describing peculiar annular densities in the chest roentgenograms of men afflicted with silicosis. These are generally seen clustered in the mediastinal region as fairly large spheroid nodules averaging 1 to 2 cm. in diameter each with a sharply demarcated apparently calcified periphery. This appearance of a thin casing around an oval-shaped body led to its apt designation as "eggshell calcifications." These calcifications are found not only in the hilar lymph nodes but also in the parenchymal portions of the lungs. They occur without any evidence of tuberculosis. One explanation for these calcific nodules is that they represent degeneration in or around silicotic nodules. Recent evidence would tend to show, however, that the calcium may represent the result of direct inhalation of the calcium dust along with silica particles. It may well be that the peculiar distribution of the calcified nodules in groups of patients with sili-



cosis from one section of the country and their absence in groups from another might be related to the environmental contact with calcium dust. This observation is of importance from a medicolegal standpoint because it indicates that the finding of calcified pulmonary lesions in silicosis does not necessarily indicate a superimposed tuberculous infection.<sup>13</sup>

### **Eosinophilic Infiltrations in the Lungs**

This condition was first described by Löffler and consists of transient pulmonary exudate associated with eosinophilia. The pulmonary infiltrations appear suddenly and disappear with equal rapidity. The size, density, and distribution are quite variable. The usual duration of the picture is between three and eight days. Eosinophilia ranges between 10 and 30 per cent but may rise as high as 66 per cent. There is no correspondence between the degree of eosinophilia and the extent of the pulmonary involvement. The associated clinical symptoms are mild. Fever is slight and pulmonary symptoms are lacking. More chronic forms of the disease have been described, however, with severe symptoms and roentgen shadows lasting for weeks or months. The roentgen appearance of the lungs, while not characteristic, often shows bands of narrow platelike homogeneous densities extending obliquely caudad and laterally, often symmetrical in the two lungs. Aside from this, the differential diagnosis may be exceedingly difficult and include tuberculosis, suppurative bronchopneumonia, or Boeck's sarcoid.

The common belief is that this condition is an allergic manifestation and it has been described as occurring in ascaris infestation and amebiasis. In other cases, bacterial toxin, food, or pollen have been thought to be responsible

allergens and the lung reaction has been considered analogous in character to the wheal formation which occurs in the skin of allergic individuals. In the chronic and more severe form, vascular damage has also been noted and a relationship between this and periarteritis nodosa may exist.<sup>14</sup>

### **Rib Fractures in Atypical Pneumonia**

In a recent review of 500 consecutive cases of atypical pneumonia, 18 patients were found to have one or more fractures of the ribs without any history of trauma. In half of the 18 cases, the fractures were multiple, and in 4 cases the fractures occurred on the opposite side from the pneumonia. All fractures occurred in the anterior axillary line and their appearance was not related to the severity of the pneumonia. It is thought that the severe, dry, irritating cough which is present in this condition is probably a factor in the production of the fractures. Extensive chest pain occurring in the course of the pneumonia should direct attention to the possible complication of a fracture rather than be misinterpreted as pleurisy as is usually the case.<sup>15</sup>

### **Intrapulmonary Lymphatic Spread of Cancer**

The lymphatic spread of metastatic cancer in the lung presents a rather unusual roentgenologic appearance, and is seen with sufficient frequency to justify greater interest than has been shown in the past. Its recognition is particularly important when the patient's early, or presenting, symptoms, are referable to the chest only. The film presents a typical pattern in the lungs which is entirely different from that of the usual pulmonary metastasis. It is characterized by a network of increased density radiating from enlarged hilar lymph nodes and

trabeculating through the lung fields in an uneven manner, and is interspersed by numerous fine nodules. It is more marked in the lower and central portions of the lung, and occasionally may be unilateral. The differential diagnoses of miliary tuberculosis, pulmonary edema and congestion, sarcoid, pneumoconiosis, and bronchiectasis must be ruled out. The microscopic picture in the lungs is characterized by widespread permeation of the lymphatic channels and, in a certain number of instances, profound arterial damage. Obliteration of the smaller arteries occurs as the result of tumor invasion by way of the lymphatics themselves. In some instances, patients have been known to succumb to right heart failure as a result of the obliteration of a large portion of the vascular bed and the secondary signs of cardiac difficulty may confuse the picture. Anaplasia of the tumor rather than its primary site appears to be the important factor in the lymphatic form of dissemination. However, most authors agree that by far the largest number of patients with this type of metastases have a primary carcinoma of the stomach.

The common clinical findings are dyspnea, cyanosis, productive cough, and rapid cachexia. The pulmonary signs are minimal but pulmonary symptoms overshadow those which derive from the primary tumor; so that it is quite natural for the diagnosis of pulmonary infection to be entertained on clinical grounds alone. In some cases, considerable relief of the dyspnea has occurred following small doses of *roentgen therapy* to the chest, in the nature of fifty roentgens daily for four or five doses.<sup>16</sup>

### Aids in the Diagnosis of Tropical Diseases

The return of large numbers of infected military and civilian personnel

from areas of endemic tropical disease may result in a significant incidence of these diseases in this country. In this connection it is well to remember that only three decades ago malaria was a common disease in the United States; typhus is still a common disease in Europe; and cholera and yellow fever are only two generations away as a commonplace in subtropical latitudes. The most important of these diseases is malaria, whose symptoms are manifold and which should be suspected in any atypical febrile illness resembling typhoid or tuberculosis. The roentgen diagnosis of an enlarged spleen seen in a survey of the abdomen may be the first lead in arriving at a correct diagnosis. The spleen may be considered to be enlarged when its shadow measures over 17 cm. in length or when its breadth is greater than 9 cm. Accessory signs are depression of the splenic flexure of the colon, depression of the left kidney, and elevation of the left half of the diaphragm. In severe chronic cases of falciparum malaria, cerebral calcifications may be seen. The next most common group of diseases are the dysenteries which give a roentgen picture of chronic ulcerative colitis. In the case of amebic dysentery, hyperplastic changes may be noted in the cecum and the appendix. When amebic abscess of the liver occurs there is often displacement of adjacent organs, particularly the stomach. In the rickettsial diseases such as typhus, a patchy type of bronchopneumonia confined to one lobe of the lung has been reported. In scrub typhus, myocardial disturbances occur and may be reflected in the fluoroscopic appearance of the heart. Infection with the parasitic worms often produces roentgen findings. Hookworm disease produces changes in the appearance and function of the small intestines, particularly the jejunum, characterized

by irritability and thickening of the mucous membrane folds. In infection with strongyloides, changes in the small bowel suggesting regional ileitis and local infiltrations in the lungs have been reported. In ascariasis, the shadow of the worms may be seen as radiolucent structures within the barium-filled small intestine, particularly the jejunum. Occasionally the intestinal tract of the worm itself may be outlined with the host barium at a twelve- or twenty-four-hour study. In filariasis, the worms may die and become calcified, producing small opacities, especially in the subcutaneous tissues, lymph nodes, and lymphatics. These appear as small linear or dotlike shadows from 1 to 4 mm. in length and only about 1 mm. in diameter. Incidentally, the pain and soreness associated with the attacks of lymphangitis which occur in this disease may often be relieved by *roentgen therapy* to the involved areas. Small doses are recommended, administered to wide fields, from fifty to a hundred roentgens, in air, with fields not less than 20 by 20 cm., with moderate filtration. The dose should be repeated every three days for about four doses. Roentgen therapy for the late complications of the disease, such as lymphuria and chyluria, has also been used with excellent results. In the disease known as dracontiasis, or infestation with the Guinea worm, long linear calcifications representing the worm in the soft tissues may be seen. Paragonimiasis is due to infestation by the lung fluke. Roentgenograms of the lungs will reveal nodular thickening of the pulmonary markings, especially in the lower lobe with variable degrees of bronchiectasis and even cavitation. Hemoptysis is a common symptom. In schistosomiasis, the ova of the parasite is often deposited in the submucosa of the urinary or gastrointestinal tract, giving rise to ulcer-

ation and subsequent calcification which can be shown roentgenographically. Two forms of reaction are seen: calcific streaks in the walls of involved areas, and oval densities like stones or calcified papillomata. Occasionally, pulmonary involvement by the schistosoma produces a picture resembling miliary tuberculosis. In tapeworm infestation, the larval form of the pork tapeworm may be deposited in many of the organs of the body and become calcified resulting in the syndrome of cysticercosis. Calcification in these larval forms rarely occurs until at least five years after infection. The calcified larvae may be found in the brain, muscles, or internal organs and usually measure 1 to 3 mm. in diameter and 2 to 10 mm. in the long axis. The larval form of the Echinococcus causes hydatid disease in man, forming large cysts which may subsequently calcify. These are found in the liver, lungs, and urinary tract; their occurrence in bone results in a patchy cystic appearance resembling osteolytic metastatic carcinoma. Infestation with the treponema results in the disease known as yaws whose peculiar tertiary forms include (a) goundou, a chronic sclerosing osteoperiostitis of the superior maxillae, and (b) gangosa, a destructive ulcerating process of the nose and palate. In leprosy, concentric atrophy of the phalanges and small bones of the hands and feet is seen, resulting in spontaneous amputation. In the condition known as ainhum, which is a neutrophic disorder, films show atrophy or disappearance of the phalanges of the toes, usually the little toe. In madura foot, which is a fungus infection, the bones and joints show varying degrees of destruction and osteoporosis as a result of the chronic osteomyelitis.

This brief summary will serve to indicate the contribution which may be made

by radiology to the study of tropical diseases.<sup>17</sup>

### Gastric Pneumography

This method of examination was first described by Engel and Lysholm in 1933 to detect enlargements of the body or tail of the pancreas. The technic is simple and should be employed more frequently because of its aid in the diagnosis of lesions which may be otherwise unsuspected. The stomach is distended with gas or air, either by the use of seidlitz powders or by insufflation through a small stomach tube. The latter method is preferable because there are no confusing fluid levels in the air-filled stomach. Roentgenograms are obtained with the patient prone and using a horizontal beam. Tumor or abscess of the pancreas shows as a dense filling defect protruding into the posterior wall of the distended stomach. Normally, the stomach will be separated from the vertebrae by a space of width equal to the vertebral body. In addition to pancreatic tumors, the following conditions may produce anterior displacement of the stomach. Tumors of the liver, metastatic nodes, inflammatory pancreatitis from perforated duodenal ulcer, hypernephroma and retroperitoneal neoplasms. However, in only pancreatic disease is the deformity of the stomach so clear-cut.<sup>18</sup>

### Hypertrophic Pyloric Stenosis in Infants

In the typical stage of this condition, the diagnosis can usually be made on the clinical symptoms and the history. There is known to be recurrent bile-free vomiting in an infant three to six weeks old with a palpable mass in the epigastrium to the right and above the umbilicus and visible abdominal waves corresponding to gastric peristaltic activity. When these clearcut findings are not present, how-

ever, differential diagnosis may be exceedingly difficult. Among the other causes of recurrent vomiting which must be differentiated from pyloric stenosis, one can list spasm or hypertonicity of the pyloric sphincter without hypertrophy, excessive amount of air in the small intestines which can result in a reflex type of adynamic ileus, and an organic obstruction below the pylorus usually in the duodenum or jejunum. Enough attention has not been paid to the condition of aerophagia and intestinal distention which is so common in the normal infant. It is well known that in the supine position, the contents of the stomach are trapped in the cardiac pouch and swallowed air progresses to the lower portion of the stomach and into the small intestines where it may accumulate in large amounts. If this is accompanied by irritability or lack of tone of the cardiac sphincter, vomiting is likely to occur. This may often be overcome by the simple procedure of keeping the infant in the prone or erect position during a large part of the time. It should be mentioned that reflex ileus as the result of disease of other organs, particularly the retroperitoneal structures, should always be borne in mind.

In the rather large group of cases in which the clinical findings are not clear-cut, the roentgen examination with barium is of invaluable aid. It should be remembered that emptying of the infant's stomach is often irregular and capricious and too much weight should not be given to the overall emptying time, particularly if the barium is administered with food or in the formula as is so often necessary. Similarly, hyperperistalsis or antiperistalsis in the stomach, or a dilation, or thickening on the wall of that organ are not reliable evidences of pyloric obstruction. In the normal infant, one should expect to see

the initiation of gastric emptying within five to ten minutes after the barium and formula has been given. In organic pyloric obstruction, this initial emptying is often delayed for from thirty minutes to sixty minutes and constitutes one of the specific roentgen signs; the other sign is the finding of an elongated and narrowed prepyloric area. The normal pyloric canal measures less than 0.5 cm. In severe cases of hypertrophy, the canal may measure up to 3 cm. and be outlined by a mere thread of barium which is constant and uniform and is not altered by the administration of anti-spasmodic drugs. Often a filling defect in the base of the cap can be seen as the result of the pressure of the tumor.

It is apparent from the above that greater care should be taken in the investigation of infants with the presenting symptom of vomiting in order that the patients who will respond to medical management may not be subjected to unnecessary operative procedures and surgical problems due to disease in the distal intestinal or retroperitoneal structures may not be overlooked.<sup>19,20</sup>

### **Antral Gastritis**

Although lesions in the pyloric and prepyloric regions of the stomach can usually be recognized by present methods of roentgen examination, nevertheless the differential diagnosis is often exceedingly difficult. Carcinoma, benign ulcer, syphilis, hypertrophy of the pyloric muscle, and antral gastritis may at some particular phase of their development so closely simulate one another that a differential diagnosis resolves itself into a matter of problematic enumeration based on the known percentage incidence of the respective lesions. The term "gastritis" refers to an inflammation of the gastric wall of as yet unknown etiology which begins in and may be limited to

the mucosa, but which frequently extends to the deeper layers, even to the serosa. The disease may be generalized throughout the stomach but is often limited to or has its maximum effect in the antrum. Here it may be found as an acute edematous process, or as an ulcerative lesion, or as an extensive chronic inflammatory process, causing induration of all the tissues down to the serosa; and it is the last type which is so difficult to distinguish from carcinoma. In antral gastritis, the patient complains of symptoms of epigastric pain, usually made worse by food, nausea, weight loss, and occasional gastric hemorrhage. The roentgen findings vary all the way from a temporary and persistent spasm of the antrum with impaired irregular and ineffective peristaltic waves producing abnormal antral systole, to a constant filling defect such as may be seen in carcinoma. If the lumen of the antrum is still patent so that a small amount of barium can be forced through, ulceration can frequently be demonstrated. Differentiation from carcinoma may be possible by gastroscopic studies and this should be resorted to more frequently in the evaluation of localized lesions in the lower portion of the stomach.

The prognosis in antral gastritis is apparently quite good, although gastric resection may be necessary because of the symptoms of obstruction. Not a sufficient number of cases have been followed to determine the incidence of gastric cancer arising on the chronic inflammatory process, although there have been several isolated case reports which indicate that this does occur.<sup>21</sup>

### **Hypertrophic Gastritis Simulating Carcinoma of the Stomach**

The difficulty of distinguishing between localized hypertrophic gastritis

and carcinoma in the stomach has long been recognized. This is particularly true of lesions in the antrum and prepyloric region and indeed some authors believe that a chronic localized gastritis eventually degenerates into malignancy. Occasionally, the localized gastritis may be present in the cardiac portion of the stomach and can form a rather large tumor which is composed almost entirely of redundant mucous membrane. Ulceration may occur with all the symptoms of bleeding and pain and the roentgen appearance often is confused with either a mucosal or submucosal malignancy. Further difficulty arises from the fact that achlorhydria is more common in this type of gastritis than it is in gastric carcinoma. It does not seem as if the diagnosis can be made accurately by roentgen study and sometimes it is impossible to make it by direct examination with a gastroscope. Surgical exploration is indicated both from a prophylactic as well as a therapeutic point of view, but one should not be surprised at the finding of an occasional pseudo malignancy.<sup>22</sup>

### **Aberrant Pancreatic Tissue**

Embryologically, the pancreas develops as buds from the duodenum. Anatomists and pathologists have long been conversant with variations in the placement of pancreatic tissue. In the roentgenologic literature, however, there is little specific reference to this problem. Duodenal diverticula may actually occur at sites where pancreatic rests produce potential weak spots in the intestinal wall. On the other hand, small filling defects in the duodenal mucosa can be produced by these islands of aberrant pancreatic tissue. Some of these filling defects may be quite large and present a very difficult differential diagnostic problem between polyps or actually car-

cinoma. On the other hand, the aberrant pancreatic tissue may be extrinsic to the duodenum and encircle it to produce a partial or complete obstruction. The complete obstruction is usually found in infancy but longstanding partial obstruction has occurred in adults as the result of this anomalous pancreatic tissue. When roentgen evidence of duodenal filling defects or compression is associated with the symptom of jaundice, it is impossible to differentiate the benign nature of the lesion from the more common carcinoma of the ampulla of Vater or the head of the pancreas.<sup>23</sup>

### **Retroperitoneal Perforation of the Duodenum**

While the diagnosis and treatment of intraperitoneal perforation of the duodenum is quite satisfactory, the reverse is true when the perforation affects the retroperitoneal portion. The majority of retroperitoneal perforations are due to trauma, usually a crushing injury. The immediate symptoms are few, and the diagnosis will be missed unless it is thought of. Pain and muscle rigidity are late symptoms, and usually indicate that free communication between the abdominal cavity and the retroperitoneal space has occurred. Laparotomy after the development of peritonitis holds scant hope for recovery.

Early diagnosis depends on clinical or roentgenographic evidence of emphysema which may develop rapidly, and the extravasated air may be seen in the mediastinum and even the neck. At early operation, the extravasated fluid material is nearly always found in one of three locations; either in the root of the transverse mesocolon, or in the root of the mesentery of the small bowel, or at both locations and in the intervening retroperitoneal space sometimes extending to the right of the kidney. The literature

reports only three instances in which this diagnosis has been made by roentgen examination, although the opportunity for a preoperative diagnosis by this means would seem to be good. In the roentgen study of this condition, administration of barium by mouth is contraindicated. It is necessary to obtain films in the erect, prone, supine, and decubitus positions with the right side uppermost in order to determine the exact location of any free air which may be seen.<sup>24</sup>

### Pseudocysts of the Pancreas

Cysts of the pancreas may be classified as true cysts when they result from the proliferation of epithelium as the result of neoplastic disease, hydatid disease, or congenital cysts; as retention cysts which occur secondary to occlusion of the duct; and as pseudocysts resulting from fluid collection secondary to inflammatory disease, or necrosis.

In the acquired pseudocysts, 7 per cent are associated with disease of the biliary tract and a high proportion of the patients have had a history suggestive of previous pancreatitis. A persistent elevation of the serum amylase after an attack of pancreatitis indicates a probable development of a pancreatic collection not from absorption of amylase from the cyst itself but from a continuation of the chronic inflammatory process in the rest of the pancreas. No quantitative relation between the serum amylase and the amylase of the cystic fluid has been found either before or after surgical drainage.

In patients with pancreatic cysts, the barium-filled stomach and duodenum may be displaced in a characteristic manner and, in addition, the cystic tumor may be outlined by means of gastric pneumograms produced by distending the stomach with air introduced through

a tube or by means of seidlitz powder and obtaining roentgenograms in the prone position with the roentgen beam horizontal.

The treatment of the pseudocyst is *surgical drainage* or *marsupialization*.<sup>25</sup>

### Physiology of the Colon

Frequently, examination of the colon twenty-four hours after a barium meal, or after evacuation of a barium enema, will show the proximal half of the bowel contracted and the distal half dilated or *vice versa*. Occasionally, instead of the above, a contraction ring is found just distal to the hepatic flexure. The point in the colon where such changes in diameter and function occur is remarkably constant in location and is situated in the proximal third of the transverse colon.

In 1902 Cannon first described a contraction ring in the transverse colon of the cat which divides the large bowel into two partitions. Later, investigators found a similar contraction ring in man and observed different functions on both sides of it: Tonic contraction and antiperistalsis in the proximal part, deep segmentation and ball formation in the distal part of the colon. It is suggested that this significant point be called Cannon-Boehm's point in honor of the early observers. Further study has failed to show any evidence of a sphincter in the transverse colon and it is proposed that this point represents the pivoting site of a change in nerve innervation between the vagus and pelvic portions of the parasympathetics, and between the superior and inferior portions of the splanchnic sympathetics. This is further substantiated by the fact that the nerves follow the blood supply and that the proximal third of the colon is served by the superior mesenteric artery and the distal two thirds by the inferior mesenteric.

This concept is important in explaining constipation of the "ascending colon type" where prolonged retention of material is due to a neuromuscular imbalance centered at Cannon's point. Furthermore, it is interesting how frequently ulcerative colitis involves the bowel only distal to Cannon's point, while tuberculosis, classically, is limited to the proximal portion of the colon. In the condition of megacolon, the extent and localization of the involvement of the large gut are especially important in the choice of operation, if sympathectomy is contemplated. The megacolon may only involve the proximal half of the bowel in which case only bilateral resection of the lumbar ganglia is necessary. When only the descending colon and sigmoid are dilated, resection of the fibers forming the inferior mesenteric and hypogastric plexuses should be done. In localized megarectum, only extirpation of the hypogastric plexus is necessary.<sup>26</sup>

### Diagnosis of Early Cancer of the Rectum

Cancer of the rectum is not often discovered in incipient stages because it rarely causes clinical signs and symptoms until it has grown fairly large. Hence every method available should be used without prejudice in making an early diagnosis. It is suggested that every effort be made to avoid irritability of the rectum and lower sigmoid by avoiding drastic purges, using antispasmodics, and administering the barium enema slowly through a flexible urethral catheter rather than a rigid tube. The barium is injected with a 20-cc. syringe under roentgenoscopic observation while the catheter is gently withdrawn towards, but not beyond, the internal sphincter. According to the degree of filling required, the opaque medium may be either added or withdrawn with the syringe.

Spot roentgenograms and Bucky films are obtained with the patient in several oblique positions. By this method an adequate study of the mucosa of the lower bowel can be done, similar to that practiced in roentgen examinations of the stomach. The earliest sign of carcinoma will be a small ulcer with rigid walls, similar to those seen in the duodenum. The mucosal pattern may appear to be erased in the immediate neighborhood of the ulcer. Similarly, small polyps which are obscured by massive filling, may be detected by this mucosal study.

The differentiation between early ulcerating cancer of the sigmoid and inflammatory disease may be difficult although thickened mucosal folds are often seen in the latter.<sup>27</sup>

### Patent Urachus

Patent urachus and urachal cyst in the newborn are not rare. These appear as a soft tissue mass protruding from the region of the umbilicus through a defect in the rectus muscles. Other anomalies of the urinary tract are frequently found. The patent urachus is a vestigial remnant of the allantois from which the urinary bladder develops. It occurs because of failure of obliteration of the embryologic tract between the developing bladder and the structures of the cord at the umbilicus. Four types have been described: Complete patency throughout; patency at the umbilical end; patency at the vesicle end; obliteration of both ends with residual cystic enlargement of the middle. Some of these cysts may develop to large size. If a communication exists between the urachus and the bladder or the umbilicus, injection of opaque media through the opening in the abdominal wall or *via* the urinary bladder clearly demonstrates the nature of the mass. Treatment consists of **surgical extirpation** which should only be



done after normal drainage of the urinary bladder *via* the urethra has been determined.<sup>28</sup>

### **Analysis of the Roentgen Appearance of the Vertebrae**

A study of fresh adult human lumbar vertebrae obtained at autopsy has shown that there is a great difference in the "shadow values" of the cortex and spongiosa. By simple experiments it was determined that most of the density of a vertebral body in the roentgenogram is due to the spongiosa, while the cortex contributes the sharp outline. It was further shown that large defects in the cortex are not recorded on the roentgenogram, but even small defects in the spongiosa can be easily seen as areas of decreased density. In 20 per cent of normal vertebrae a linear area of decreased density bisecting the body in the transverse plane is visible on the roentgenogram. This is formed by the central reservoir of the sinusoidal vertebral veins, which is especially well developed.<sup>29</sup>

### **Vertebral Changes Accompanying Spinal-Cord Anomalies**

That the spinal canal may be markedly dilated as the result of an intraspinal neoplasm is well known, but that an equally pronounced dilation may occur at any level as a result of a congenital anomaly of the cord structures is not generally recognized. Most of the lesions of myelodysplasia occur in the caudal portion of the cord and one of the commonest is a diffuse lipoma infiltrating the roots of the cauda equina and associated with a spina bifida occulta and a small mass over the sacrum. Other anomalies such as a single nerve trunk instead of the cauda equina, or the presence of dermoid cysts or adhesive bands, may be encountered.

The roentgen appearance of widening or spreading of the vertebral pedicles is of great help in localizing the lesion. In contradistinction to the finding in tumor, this increase in the interpedicular distance is not the result of an expanding lesion, but occurs very early in embryonic life and is thought to be due to a failure of the normal "migration" or upward shift of the spinal cord in relation to the vertebral segments.

Symptoms of increasing weakness in the lower extremities and bladder control occur early in the patient's life. Surgical exploration is advised, but often the anomalies are too extensive to be corrected.<sup>30</sup>

### **Infantile Cortical Hyperostosis**

Recently there have been reported four cases of what is believed to constitute a new syndrome in pediatrics. The principle features of the disorder include:

Onset in the early part of the first year; tender swelling in one or more of the following sites—face and jaws, scapular region, and extremities; and multiple scattered hyperostoses demonstrated roentgenographically in bones adjacent to the tender swelling and also in several other bones whose overlying soft tissues appear to be normal clinically and roentgenographically. Several of the infants also developed a transient pleurisy with effusion associated with periosteal proliferation along the margins of the ribs. The active manifestations subsided completely after several weeks and there were no serious complications. Although fever was present, it was irregular and inconstant. The most unusual features of the syndrome were the rapid appearance of the swellings which often attain considerable size in a few days and subside gradually after many weeks. The cortical thickenings along the tubular bones also appeared in a remarkably

short time and gradually diminished until they could no longer be identified several months afterward.

The common causes of periostitis have been eliminated. No history of trauma was obtained and the feeding history of both mother and infant showed an adequate intake of vitamin C in all cases.



Fig. 4—Massive cortical thickenings of the right radius and ulna of white male at five months of age, the bones of the hand are not involved. Note the absence of metaphysical changes suggestive of scurvy. (J. Caffey and W. A. Silverman: *Am. J. Roentgenol.* 54: 1 (July) 1945.)

Furthermore, the roentgen appearance of the bones was not compatible with a diagnosis of scurvy. Syphilis also could be excluded by the uniformly negative blood serology and the lack of the clinical or roentgenographic evidences of syphilitic osteomyelitis. No bacterial infection could be proved either by biopsy of the bone or skin lesions, or by culture. The possibility of a response to a virus infection or to an allergic state in the subperiosteal tissues has been mentioned as an explanation although no actual

proof has been forthcoming as yet.<sup>31</sup> (Fig. 4.)

### Osteochondritis Dissecans of the Elbow

Occasionally, roentgenograms of an elbow will show irregular areas of decreased density in the thin portion of the humerus just above the condyle known as the supratrochlear septum. This appearance has been thought in the past to be due to accessory centers of ossification or a tiny sesamoid bone. The operative findings in six cases presenting this roentgen appearance have shown that the lesion is really an osteochondritis dissecans. Inasmuch as these patients all showed either an actual foramen in the supratrochlear region of the normal elbow or a very thin cortical plate, it is thought that a vascular abnormality during growth is a predisposing cause for the osteochondritis. It is known that symptoms may not exist or remain subclinical for a considerable time. The minimal trauma associated with the onset of clinically noticeable symptoms cannot be considered the major cause of the condition. Extrusion of the diseased cartilage as a loose body in the joint may occur. Surgical removal affords complete relief of symptoms.<sup>32</sup>

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## SURGERY

### ABDOMINAL SURGERY

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#### APPENDICITIS

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**Incidence**—Relationship between age and types of appendicitis is well illustrated by the following table which serves to support the view that perforation of acutely inflamed appendix tends to occur earlier in the course of disease in babies and young children. Perforation was encountered more than twice as often as was simple acute appendicitis without rupture. All patients under two years of age had perforation.

**Etiology**<sup>1</sup>—Obstruction of the appendiceal lumen may be produced by several pathologic entities. Wangenstein was able to demonstrate the presence of Gerlach's mucosal fold in 80 per cent of over 500 cadavers and also, by microscopic study of the cecoappendiceal junction, the existence of a sphincter-like group of circular muscle fibers at

RELATION BETWEEN TYPE OF APPENDICITIS  
AND AGE

<i>Acute Unruptured</i>		<i>Acute Ruptured</i>	
<i>Age in Years</i>	<i>No. of Cases</i>	<i>Age in Years</i>	<i>No. of Cases</i>
0- 1	1	0- 1	0
1- 2	0	1- 2	22
2- 4	15	2- 4	59
4- 6	37	4- 6	42
6-12	195	6-12	109
12-16	24	12-16	2

(Scott, H. W., Jr. and Ware, P. F.: *Arch. Surg.* 50: 258 (May) 1945.)

the appendiceal base. These two factors offer some resistance to the outflow of luminal secretions, which cause fecaliths to be the most positive cause of appendiceal obstruction. Concretions were found in 40 per cent of all appendices

in the Children's Hospital series on pathologic examination. In 66 per cent of specimens exhibiting perforation, fecaliths were present. The actual figure of incidence is probably much higher than this. Obviously, by the time of operation the fecalith may already have been extruded into the cecum or into the general peritoneal cavity through a perforation. Unfortunately, the presence or absence of a fecalith in the peritoneal cavity has not been specifically recorded in most of the operative notes.

Another factor which may predispose to the development of acute appendicitis in children is infection of the appendix with pinworms (*oxyuris vermicularis*). These parasites were present in the appendices of sixty patients presenting the clinical picture of acute appendicitis in this five and one-half year period. In twenty-five of these patients there was acute inflammation of the appendix, with perforations in four instances. The appendices of the remaining thirty-five who had a typical clinical picture of appendicitis showed no gross or microscopic inflammatory changes, and their cases are not included in this series. The relationship of pinworms to appendicitis was discussed by Botsford, Hudson, and Chamberlain in 1939, but no definite conclusions as to the etiologic connection could be formed. Nevertheless, it is possible that a bolus of pinworms may occasionally obstruct the appendiceal lumen in the same way a fecalith does.

**Diagnosis**—The typical attack in a young adult is ushered in by pain apparently due to overdistention of the appendix. It partakes the nature of a sustained colic. The pain can seldom be exactly located but is referred to the center of the abdomen, the region of the umbilicus, or the epigastrium. It varies from an almost unbearable ache to a feel-

PATHOLOGICAL DISTRIBUTION

Appendicitis, acute suppurative simple.....	645	} Perforative Appendicitis 73 Cases
Appendicitis, acute perforative with abscess.....	34	
Appendicitis, acute perforative with general peritonitis	39	
Total acute suppurative appendicitis.....		718
Interval appendicitis.....		610
Incidental appendectomies.....		154
Carcinoid of the appendix.....		4
Actinomycosis appendix.....		2
Tuberculous appendicitis.....		1
Decidual reaction ..		3
Oxyuris in appendix.....		2
Total appendectomies.....		1,494

(Fisher, H. C. and Burch, J. C.: South. M. J. 38: 255 (April) 1945.)

ing of nagging discomfort but is usually severe and associated with nausea. Very rarely it is relieved temporarily by passage of gas or a movement of the bowels. Keyes<sup>3</sup> emphasizes the importance of "gas stoppage" as a basis for diagnosis during the first phase. The gas stoppage merits the name because it is always a desire to pass gas downward rather than up and characteristically gives little relief from the general abdominal tormina or discomfort. Keyes<sup>3</sup> claims that this symptom was present in forty out of fifty proven cases of appendicitis. The other condition producing similar symptoms is intestinal obstruction. After several hours the sensation of gas stoppage subsides and is exchanged for a feeling of soreness in the right iliac fossa, in the region of the appendix itself.

Accurate diagnosis of appendicitis is often difficult. Many diseased appendices perforate while an even larger number of normal ones are removed on suspicion. Because of difficulty in diagnosis and fear of subsequent attacks, some

extremists have gone so far as to advocate removal of all appendices. Observation of a patient on an hourly basis is not dangerous.

There are a few facts about clinical manifestations<sup>4</sup> which will aid tremendously in solving the diagnostic problems. In the first place, pain always precedes nausea and vomiting in appendicitis. About the only exceptions are those rare instances when appendicitis develops secondarily to an acute enteritis. The presence of diarrhea to a great extent excludes the diagnosis of appendicitis, although there are occasional instances when the acute enteritis may give rise to appendicitis. Vomiting itself is a relatively late symptom and seldom is present to a severe degree. Appendicitis may proceed to perforation without vomiting, particularly in retrocecal appendicitis in which vomiting is rare. By far the great majority of cases of acute appendicitis reveal a leukocytosis, but we have exceptions in so far as the appendix may perforate without evidence of leukocytosis. Another fairly consistent rule is the absence of significant fever until the point of perforation or after. A low grade fever up to 100° F. may be present even in the early stage of appendicitis, particularly in children. However, the presence of a fever above 103.5° F. and 104° F. excludes unperforated appendicitis. In other words, if the local findings are so meager as to exclude perforation, then a high fever accompanying these findings can actually exclude the diagnosis of appendicitis. In such instances, when high fever is present with minimal local findings, urinary infection will be one of the most common explanations of the clinical picture. An error in diagnosis is not of great consequence so long as the physician makes the correct decision as to whether or not an operation was needed or indi-

cated. On a few occasions, operation is performed largely as a protective measure when appendicitis cannot be excluded in the diagnosis. This is justifiable when you realize that under such circumstances the mortality rate following the operation will be much less than  $\frac{1}{2}$  of 1 per cent, whereas it may be over 10 per cent if operation is delayed until the time of perforation.

In retrocecal appendicitis, many of the signs and symptoms are unreliable. It is common to have retrocecal appendicitis progress through the point of perforation without muscle spasm or nausea and vomiting. However, leukocytosis will be just as constant in retrocecal appendicitis as in any other type. One of the most valuable signs in the identification of retrocecal appendicitis is pronounced local tenderness posteriorly or laterally in the iliac fossa. However, we must be able to exclude the urinary tract as the offending source of the trouble.

Malloy, Jason, and Drew<sup>5</sup> emphasize the differential diagnosis of lymphoid mesenteric hyperplasia. Fifty-seven cases were characterized by a history of an upper respiratory infection or gastrointestinal upset for a few days to a week or ten days, and gradually or suddenly developed colicky abdominal pains. In many cases, the preceding infection may have only a brief interval between its onset and the onset of abdominal symptoms. The abdominal pains may begin and end in the right lower quadrant, or they may be generalized at first, and later become localized in the right lower quadrant, findings which are common in appendicitis in general. The attacks are usually recurrent and the increased frequency or increased severity of the abdominal symptoms forces the patient to seek relief. Nausea and vomiting are usually present and the occur-

rence of anorexia is found in every case in which the inflammatory process in the appendix is severe. The white blood count is usually below 10,000, but again when the primary infection is present and inflammation has been added to the appendix, the white blood count is influenced by this and is above 10,000 in the majority of cases. In this series, many of these patients when first seen were considered as cases of acute mesenteric lymphadenitis or subsiding appendicitis, yet they were operated upon in order not to incur the risk of overlooking an irreversibly inflamed appendix. It is the conviction of Malloy, Jason, and Drew<sup>5</sup> that it is to invite disaster to discharge a patient with a diagnosis of acute mesenteric lymphadenitis without a period of observation.

**Appendicitis in Childhood**<sup>6</sup>—The warning signal of abdominal pain ("stomach ache") can never be dismissed casually, and its presence calls for exclusion or establishment of the differential diagnosis of appendicitis in the greatest majority of cases. The generalized pain or tormina in the abdomen, followed in a few hours by localized point tenderness over McBurney's point, is probably the most important diagnostic sign. A frequent cause of confusion in the differential diagnosis lies in the abdominal pains that occur with parenteral infections, most often with upper respiratory tract infections, possibly only because these are more frequent than all other infections combined. They occur not infrequently with acute rheumatic fever. One type of pain occurs early, is commonly restricted to the umbilicus, is sharp, intermittent, of variable intensity, and suggests a referred pain from some undetermined source. There is little or no tenderness. Another pain occurs at any time during, or throughout, the parenteral infection, is more diffuse, of

a duller character, and there is more tenderness than spontaneous pain. This pain is rather obviously due to mesenteric lymphadenitis. This has been confirmed by both operation and necropsy. If the pain and tenderness are widespread or on both sides, the case is probably not one of appendicitis. Whether these two manifestations of pain have a common origin is not known. One can only speculate as to whether this more widespread type of lymphadenitis has the same etiology as the mysterious, apparently more regional, lymphatic involvement not so infrequently encountered at operation instead of a suspected appendicitis. Brennemann<sup>6</sup> doubts it himself. It has been claimed that the differential diagnosis between appendicitis and lymphadenitis can readily be made by turning the patient for a short time on the left side and then determining the site of tenderness. If it remains on the right side, it is said to be due to appendicitis; if it has shifted to the left side, to lymphadenitis. Brennemann has not been able to confirm this sign in children, nor does he know how to differentiate the two conditions. It should be emphasized, although parenthetically, that the presence of an upper respiratory tract infection must never keep one from treating as appendicitis a condition that looks like appendicitis, since there is considerable evidence that more than half of all cases of appendicitis are causally related to throat infections.

Mortality in childhood appendicitis is recorded by Anderson<sup>7</sup> of Australia. The figures are concerned only with those cases of appendicitis proved at operation or postmortem. From among 878 patients between three and fourteen years of age, covering the period from July, 1931, to June, 1943, 24 died—a mortality rate of 3 per cent. Twenty-two of these deaths occurred in cases

complicated by peritonitis or appendiceal abscess. The mortality rate bore no relation to the manner of drainage or lack of drainage of the abdomen. Among forty-one cases accompanied by peritonitis or abscess, thirteen were under two years of age and eight of them died. Of the remaining twenty-eight over two but under three, eight died.

**Appendicitis in Pregnancy**—Johnson<sup>8</sup> reports that the incidence of appendicitis in women is not influenced by pregnancy. Primary acute appendicitis occurs at the same rate in all women irrespective of whether a pregnancy is present or not. Although primary acute attacks of appendicitis are rare in pregnancy, an existing chronic appendicitis is unfavorably influenced by it. The course of acute appendicitis during pregnancy is rapid and perforation may occur within a few hours, especially in the later months. Diagnosis becomes increasingly difficult after the sixth month. When doubt exists, operation should be performed if the patient's general condition is grave. With early operation, the maternal prognosis is good, but if perforation has occurred a mortality rate of 50 per cent must be expected. There is little danger of abortion in simple cases, but after perforation 50 per cent of uteri will empty themselves, thus increasing the mortality by 5 per cent. In the last two months, perforation is extremely dangerous both to mother and to child. Cesarean section followed by appendectomy is advocated as the procedure most likely to give good results. The type of cesarean section depends on the extent of involvement of the parietal and uterine peritoneum. If involvement is very severe, Porro's operation is safest. In most other cases, the lower segment operation will be best. Whenever possible, the diseased appendix should be removed

if there is a possibility of the occurrence of pregnancy.

**Treatment**—Disagreement exists regarding the use of delayed or conservative treatment in appendicitis. There is likewise an equal amount of misunderstanding of facts in so far as physicians erroneously treat certain cases conservatively, having misinterpreted the indications for conservative therapy. In one feature there is no disagreement, namely, that appendectomy should be performed in every patient up to perforation of the appendix and several hours beyond. The controversy arises in the group who have perforated longer than eighteen to twenty-four hours. Cole<sup>4</sup> believes that with the availability of *sulfonamides* and *penicillin* we will be able to state that any patient with appendicitis who is not developing early evidence of mass formation should be subjected to immediate appendectomy. The one exception is that an operation must not be performed if it appears that laparotomy itself would be sufficient to produce a fatality. On occasions, treatment by intravenous *glucose* and *saline*, which would reestablish fluid and electrolytic imbalance, will change the situation from one of inoperability to operability in a few hours. Conservative treatment consists of *Wangensteen decompression*, *intravenous fluids*, *sulfonamide* or *penicillin* therapy, and simple *drainage* of the *peritoneal cavity*, under local anesthesia, if the patient's condition is critical. Never drain an appendiceal abscess across from the free peritoneal cavity. When one is faced with the problem of extreme toxicity,<sup>1</sup> considerable clinical judgment is required, and it is essential to recall that removal of the ruptured appendix offers the patient the greatest assistance in overcoming his infection. Ochsner and Johnston<sup>9</sup> make a plea for careful study

and individualization in every case of appendiceal peritonitis. They advocate: (1) Immediate surgical extirpation of the vermiform appendix in all cases of unruptured appendicitis; (2) immediate appendectomy in all patients with ruptured appendicitis in whom there is not definite and demonstrable localization; (3) conservative therapy of all cases of localizing inflammatory processes until abscess formation, followed by surgical drainage. When the appendix is incorporated in the wall of the abscess and cannot be removed without destruction of the inflammatory barrier, with subsequent generalized peritoneal infection, Scott and Ware<sup>1</sup> suggest that simple drainage should be instituted and appendectomy deferred for about six months.

Stratte<sup>10</sup> advocates inversion of the stump of the appendix in the following manner: "After tying the mesoappendix and cutting it away from the appendix, the site selected for amputation is not crushed. It is tied off at a distance of about one-third inch from the cecum with a plain No. 0 catgut, using a granny knot (the idea being that a few hours later the knot will open into the lumen of the gut). A purse-string suture is placed about the appendiceal base, using No. 000 or No. 0000 chromic on an atraumatic needle and placing the first stitch in such a manner that when the purse-string suture is tied, the appendiceal artery will be included in the tie. Then a Kelly forceps is slipped under a loop of the purse-string suture opposite the ends to be tied and a bite is taken into the appendix just proximal to the constriction made by the tie which tied off the appendix. Now an artery forceps is placed across the appendix just distal to the tie and amputation is consummated between the tie and the distal forceps either with an electrocautery or a knife followed by phenol

and alcohol. The purse-string suture is tied by the surgeon, while the assistant uses the Kelly forceps, with its grasp on the stump as described, to complete the inversion. More stitches may be added at the discretion of the surgeon."

**Sulfanilamide Therapy**—Postoperative period following appendectomy for acute nonperforative appendicitis in children presents few problems. Scott and Ware<sup>1</sup> have used chemotherapy postoperatively only when smears or cultures of the peritoneal fluid taken at operation have revealed organisms. They report that while no definite statistical conclusions can be drawn from the figures, it seems that in their cases the intraperitoneal use of sulfonamide compounds offered no great advantage over the oral or parenteral use of *sulfathiazole* or *sulfadiazine* in reducing the incidence of these complications.

Ochsner and Johnston<sup>9</sup> report that comparison of treatment and results in the years 1933 and 1943 indicates that therapy now employed is more effective than that used formerly. Sulfonamide drugs have been a boon in lowering mortality and morbidity. They should be used as supplement to rather than replacement of surgical judgment. Equally important, however, are the use of relatively large amounts of *blood* and *plasma* and routine employment of gastrointestinal decompression in all cases with any possibility of adynamic ileus.

According to Mueller,<sup>11</sup> *sulfanilamide* has been used locally in 320 out of a total of 739 cases of acute appendicitis and its complications during the past five years. The mortality in this group of cases was 0.4 per cent. The postoperative complications were relatively few. In a similar group of cases in the five-year period before the use of local sulfanilamide, 742 cases were operated upon, with a mortality of 2.83



per cent, and there were considerably more complications. No serious toxic effects followed the use of sulfanilamide locally in the peritoneal cavity. Local use of sulfanilamide is preferred to the use of sulfonamides orally or intravenously, because of the high local concentrations of the drug in the peritoneal cavity.

**Early Rising**—Patricelli<sup>12</sup> states that during the last two years, all those patients who would cooperate were subjected to the following regime: The patient was mentally and psychologically primed that no harm would result, that early rising was the logical procedure, that normal excretory function would be more quickly resumed, that there would be less gas pain, that there would be less catheterizations required and that less pulmonary complications, such as atelectasis, pneumonia, and embolism would occur. The patient was asked to move very freely in bed with no fear of any untoward consequences.

**Complications**—The most common complication of appendicitis is *peritonitis*. The treatment of peritonitis caused by a perforated appendix is a bit controversial. In Cole's<sup>4</sup> estimation, any patient with peritonitis produced by a perforated appendix, presenting no evidence of localization by abscess formation, should have an *appendectomy* to eliminate the source of the peritonitis, unless he is so ill that operation would produce a fatality. Such a policy seems particularly justifiable now, since *sulfonamides*, *penicillin*, and *streptomycin* are available. Nevertheless, it should be emphasized that no drug could be expected to overcome a continuous contamination resulting from a constantly leaking appendix.

Treatment of generalized peritonitis by the newer method of drainage in gross perforation of the appendix has

rewarded efforts by reduction of the mortality. The Babcock sump drain, reported by Burnett, Rosemond, and Caswell,<sup>13</sup> lends itself most readily to cleansing and sterilization. The drainage tube is made of stainless steel and causes no demonstrable irritation to tissue. It should be placed into the most dependent part of the infected cavity. The patient's position should promote gravity drainage of exudate into this dependent area. Only liquid exudate is subjected to the vacuum. No direct suction is made at any time against bowel, omentum or soft tissue unless dressings are erroneously permitted to seal the protruding end of the larger tube. It is essential for proper functioning of the drain that there be free access of air and that there be sufficient space between the inner aspirating tube and the outer collecting tube to allow for its passage or else vacuum against bowel and omentum will occur. Simple tests should be made frequently to insure proper function of drain, bottle, and motor. If the vacuum gauge rises above zero, there is blockage.

In addition to the important factors of decreased mortality and morbidity, other advantages of sump drainage are: (1) Removal of pus by positive means from the bottom of cavities instead of puddling and overflow from accumulation and body or intestinal movements as obtains with other methods. Thus even large but localized abscesses are more rapidly healed. (2) Frequent change of the small dressing is usually not required. (3) Ventilation and more adequate drainage decrease odor which is an important esthetic factor to many patients. (4) Pus is collected in a bottle with or without deodorant or antiseptic for easy disposal instead of on the dressings, etc. (5) Postoperative hernia is much less likely. Burnett, Rosemond,

## NINETY-SIX CASES OF GROSS PERFORATION OF APPENDIX

	<i>Number of Cases</i>	<i>Hospital Stay*</i>	<i>Duration of Fever Above 100° F.*</i>	<i>Duration of Drainage*</i>	<i>Number of Deaths</i>	<i>Mortality Per Cent</i>
Pre-sump-sulfonamide era.....	34	15.4	5.1	7.2	12	35
Sump-sulfonamide era.....	62	18.9	5.46	5.53	6	9.6
Sump drain and appendectomy without sulfonamides.....	14	15	3.6	4.3	0	0
Sump drain and appendectomy with sulfonamides.....	33	16.6	4.87	4.63	5	15.1

\* Average number of days.

(Burnett, W. E., Rosemond, G. P. and Caswell, H. T.: S. Clin. North America 24: 1316 (Dec.) 1944.)

and Caswell<sup>13</sup> state that only two small ones were discovered at reoperation for appendectomy, although they were not demonstrable before incision. (6) Post-operative obstruction is less likely. (7) Postoperative secondary abscesses are rare.

*Abscess of the peritoneal cavity*<sup>4</sup> is a common complication of perforated appendix. Failure to perform a rectal or vaginal examination commonly is the explanation of lack of recognition of abscess in the pelvis. *Subdiaphragmatic abscess* is a relatively common complication of perforated appendicitis. The most reliable and sometimes the only indication is the development of fever. The most reliable evidence of subdiaphragmatic abscess is elevation of the diaphragm with fixation, as determined by fluoroscopy. *Intestinal obstruction* is a late complication of appendicitis, usually occurring after adhesions have formed and the acute symptoms have disappeared. Obstruction of this type responds to intestinal decompression, although the obstruction is apt to recur after relief is obtained. If the obstruction should occur early in the disease before the inflammatory process has cleared, it would be particularly important to avoid operation

if possible and rely upon control by decompression.

Scott and Ware<sup>1</sup> report that in seventeen cases this complication appeared during the first or second week after operation, while in two cases late obstruction occurred five and twelve months respectively following peritonitis. Early intestinal obstruction is usually a result of friable, fibrinous adhesions due to plastic exudate between loops of bowel. In the earlier cases of Scott and Ware's series, Witzel enterostomy was done without delay, but this has been rarely necessary in recent years. Resorption of exudate with relief of the obstruction will take place in most instances within a few days if decompression of the distended bowel is accomplished by constant gastric siphonage or the use of a Miller-Abbott tube. High concentration oxygen is also of definite value in this regard. For late intestinal obstruction, laparotomy and lysis of adhesions are clearly indicated.

Hughes and Lambeth<sup>14</sup> present a table on *pulmonary complications* following 361 appendicitis operations:

Atelectasis alone or with pneumonitis.....	5
Bronchopneumonia or bronchitis.....	7
Lobular infarct .....	1

Pulmonary complications were present in 10.4 per cent of the 49 operations for severe appendicitis and 2.6 per cent of 312 operations for uncomplicated appendicitis.

There are few reported cases in the medical literature of the formation of large *calculi in the appendix*. The two largest appendiceal calculi known are one reported in 1921 by Packard, measuring 1.0 by 2.0 by 4.0 cm., and the one reported by Bunch and Adcock in 1939, measuring 2.75 cm. in each direction. Pilcher<sup>15</sup> adds his findings of a calculus that measured 2.75 cm. in diameter. As far as can be determined, these three cases are the only ones of true calculi of such large size found in the appendix.

*Appendicostomy*<sup>16</sup> is useful for the relief of obstruction due to a carcinoma of the left colon or as a complemental operation in resection of the bowel. The Devine defunctioning procedure may be dangerous when the transverse colon is tense and thinned from distention by fecal material. It then is difficult to suture the arms of the loop together without tearing or puncturing the bowel or to exteriorize the ends of the divided bowel without contaminating the subcutaneous fat. The clamps devised may not be suitable for the individual patient; sinuses or fistulas may persist from the two segments of bowel left implanted in the abdominal wall, and the final closure may greatly prolong the patient's hospitalization. As a rule, Babcock and Bacon<sup>16</sup> prefer a simple appendicostomy or cecostomy. The appendix and mesoappendix are pulled through a small stab wound at McBurney's point and a 14 or, preferably, a 16 French rubber catheter passed into the cecum and tied in. The mesoappendix remains attached to nourish the portion of the appendix within the abdominal wall. The catheter should be tied in with two ligatures,

anchored by tying them over dental cotton rolls, and then tested by irrigation to prove its position within the cecum. Unless carefully anchored and viable, the section of appendix may slip back into the abdomen. For decompression, the colon may be frequently irrigated with 1:10 solution of hydrogen peroxide. After the appendix has adhered in the wound it may be dilated by the daily introduction of catheters of increasing size until, if desired, a 26 or 28 French is in place.

*Mortality*—Cole<sup>4</sup> points out that although there has been a sharp decline in the mortality rate in acute appendicitis, it still remains a serious disease. The death rate per 100,000 population in the United States has dropped from a high of 15 between 1925 and 1930 to 5.4 in 1944. It is well known that the mortality rate in the mild case of appendicitis is extremely low, being less than one-half of 1 per cent, contrasted to a figure of 10 to 15 per cent in the perforated group. The mortality rate itself began to show a sharp decline with the use of sulfonamides, and will no doubt show a still more precipitous decline with the use of penicillin. Early diagnosis and operation are the important factors for lowering the mortality rate of appendicitis in children.<sup>17</sup> More harm can result from the delay of operations than from operations performed on an erroneous diagnosis. In Scott and Ware's<sup>1</sup> series of 506 cases, 8 deaths occurred, a mortality rate of 1.58 per cent. In their series of 234 cases of perforated appendices, 7 deaths resulted, a mortality rate of 2.99 per cent. These deaths occurred in children with generalized peritonitis.

In a report on 23,000 cases studied from the Pennsylvania state-wide hospital records of 1942, Bower<sup>8</sup> states that the mortality of patients suffering with spreading peritonitis, the result of a

	<i>Sulfonamides Administered</i>			<i>Sulfonamides not Administered</i>		
	<i>Cases</i>	<i>Deaths</i>	<i>Mortality Per Cent</i>	<i>Cases</i>	<i>Deaths</i>	<i>Mortality Per Cent</i>
Drained . . . . .	408	139	34.07	76	32	42.11
Not drained . . . . .	34	22	64.71	6	3	50.00

perforated appendix, in 186 hospitals in 1937 was 25.96 per cent. The mortality of spreading peritonitis in these same hospitals in 1942 was 41.17 per cent. The most conclusive evidence available regarding the results of removal or non-removal of the perforated appendix complicated with spreading peritonitis is the record of hospitals in the state where a minimal mortality has been consistently maintained by doing as little surgery as possible in the presence of a fulminating peritoneal infection. The appendix is not removed or searched for, drains are inserted, and the wound not sutured. In many of these hospitals absolute Ochsnerization is instituted, operation is deferred until a localized abscess develops, the appendix not removed, and the drains not disturbed before the seventh day. In contrast to the above, a review of the results of management in the hospitals where an appendectomy was performed immediately regardless of degree of peritoneal involvement showed a consistently higher mortality.

It may be that the surgeons in charge of these patients were so impressed with the apparently favorable results obtained with the use of sulfonamides in some patients that they expected miracles when a large amount of the drug was placed in the peritoneal cavity in severe types of infection. In the drainage group, those who received sulfonamides showed a lower mortality but the patients in this group who did not receive the sulfonamides comprised but 19 per cent of the sulfonamide group. While the deaths in

the group without drainage might be attributed to the absence of drains, it is rather significant that the patients who had the drug placed in the peritoneal cavity showed a 14.71 per cent higher mortality. It is also significant and bears repetition that a review of the patients with spreading peritonitis who were not operated on shows that the only recoveries occurred among those who did not have the sulfonamides. Of the thirty-two patients admitted to hospitals with a diagnosis of spreading peritonitis of advanced degree and not operated on, fifteen were given the sulfonamides and all died; seventeen were not given the sulfonamides and two lived.

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## BILIARY DUCTS

FREDERICK A. FISKE, B.S., M.D., F.A.C.S.

### Stricture

It is pointed out by Allen<sup>1</sup> that the injuries to the common and hepatic ducts occur with greater frequency than is usually admitted. Many of these technical errors are unrecognized as the cause of death. Those who survive are doomed to a shortened life or invalidism and repeated operations. The so-called liver death due to ligation of the right hepatic artery is mentioned. The frequent anomalies which occur in the region of the duct and vascular supply to the gallbladder should be studied at the time of operation and all structures clearly identified before division. The author felt that dissection of the gallbladder from above downward, aided by an artificial edema in the gallbladder peritoneum, was helpful in accurately identifying the ducts and other important structures. The cystic artery, cystic duct, and common hepatic duct should all be identified before any structure is clamped. Early recognition of an injured bile duct is essential and should be repaired at the time of injury. Careful approximation of the ends of the duct over a "T" tube or "L" tube which is brought out through the duct at a

distance from the anastomosis, so that it will lessen the damage at the site of anastomosis and decrease the incidence of postoperative stricture, was advocated.

The victims of injured bile duct fall into two main groups: (1) The type that becomes jaundiced within a few days after operation, or drains an unexpected amount of bile into the peritoneal cavity or to the outside; (2) those patients who do moderately well for some weeks or even months before developing signs of jaundice with beginning episodes of chills and fever. In the first group the ducts have usually been divided and the cut ends ligated. Temporary relief may be obtained within a week or ten days by the sudden outpouring of large quantities of bile after the suture has been disturbed. Others, approximately 25 per cent, die from a bile peritonitis. If drains have been adequately placed, excessive biliary drainage may occur and the patient survives. The group with ligated ends should be subjected to corrective surgery before the sutures have given away. This accident is apt to take place when the cystic duct is short or runs to the common duct at a low level. Traction on Hartman's

pouch brings into view a normal size common duct that under tension seems to the operator small enough to be the cystic duct. It is difficult to explain how the surgeon can tie the same duct at a higher level, which must be done in order to liberate the gallbladder, without recognizing this error. Another injury is tenting of the common duct, allowing complete division of the structure. This

ally produces invalidism which requires surgical assistance in about six to eighteen months. In these cases the distal segment of the duct is often narrow and sclerosed into a fibrous cord. Exposure of the ampulla of Vater through the duodenum shows that a very fine probe cannot enter the duct. The author did not feel that these cases were amenable to end-to-end anastomosis.

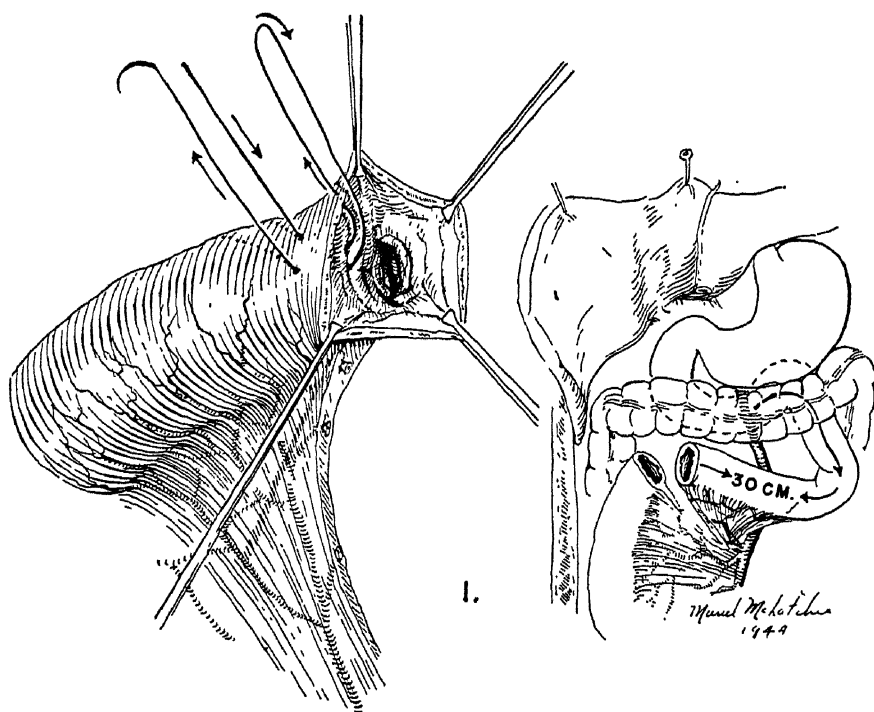


Fig. 1—Schematic drawing representing the division of the jejunum approximately 30 cm. distal to the ligament of Treitz. Also the method which is used to invert the end of the distal segment. (Allen, A. W.: *Ann. Surg.* 121: 412 (April) 1945.)

condition usually permits an end-to-end anastomosis. In group 2, partial strictures take place when the duct is tented sufficiently to constrict its anterior portion. Injury to the duct may also occur during a blind attempt to control an unexpected hemorrhage. If a sudden hemorrhage occurs, the author emphasized moving to the left of the table placing the fingers in the foramen of Winslow and compressing the hepatic vessels until the exact site of bleeding can be determined. Partial duct injury usu-

It was felt that two factors were involved in explaining the reason that anastomoses between the gallbladder or duct to the gastrointestinal tract often result in cholangitis. (1) The peristaltic action of the gastrointestinal tract which tends to send its contents into the liver ducts; (2) a gradual narrowing of the communication with inspissated bile or actual stones contributing to the inflammatory reaction. All of the successful operations have been based on a wide, free, and permanent communication. Re-

ardless of the method employed, the following points are important in re-establishing continuity.

(1) The elimination of scar tissue and prevention of its recurrence at the anastomosis; (2) an isoperistaltic anastomosis with the gastrointestinal tract; (3) nonabsorbable interrupted sutures; (4) watertight closure at the anastomosis; (5) holding the anastomosis temporarily by some tube.

ences with the vitallium tube were not entirely satisfactory.

When the distal end of the duct is sufficiently destroyed to make an end-to-end anastomosis impractical, the author advocates anastomosis of the remaining proximal duct to the end of the jejunum as illustrated.

This method of repair was used in eight cases, three of which had one or two mild transient episodes of pain, jaun-

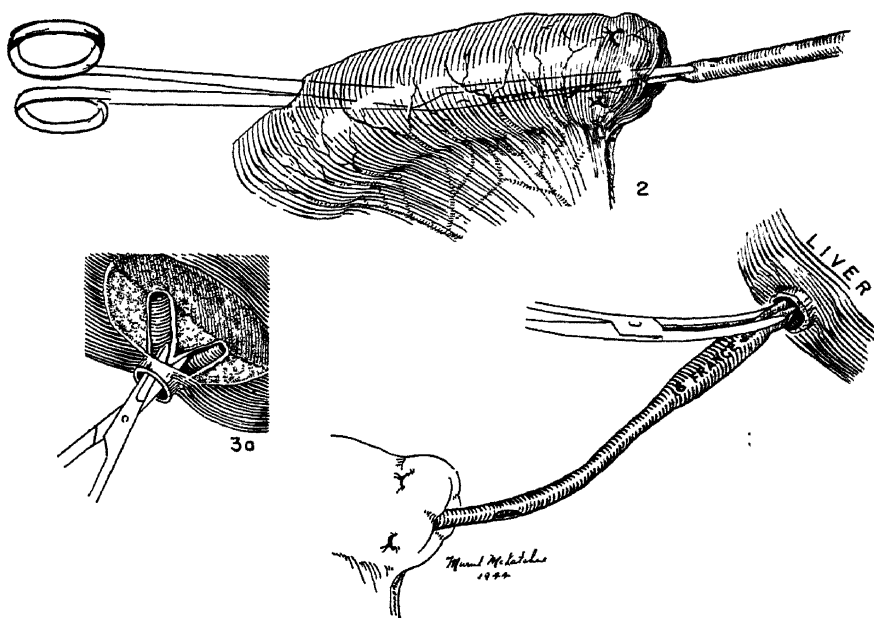


Fig. 2—Schematic drawing to illustrate the turned-in distal segment of the jejunum and how the catheter is brought down through the lumen of the intestine.

Fig. 3—Illustrates a method used in three instances to increase the depth of the hepatic duct so that at least 1 cm. of the bell end of the catheter could be held into the remaining segment of the duct. Note the eye cut in the catheter to allow bile to seep into the intestine instead of all coming through the tube to the outside.

Fig. 3a—Illustrates the method of introducing the bell end of the catheter into the developed segment of the hepatic duct. (Allen, A. W.: *Ann. Surg.* 121: 412 (April) 1945.)

It was pointed out that the use of a vitallium tube had these disadvantages: The inability to dilate, the possibility of being dislodged into the gastrointestinal tract, and the possibility of obstruction to the tube by means of deposited bile salts. This may be prevented by the free use of bile salts during the post-operative period. The author's experi-

dice, chills, and fever following the operation. Patients have been observed over a two-year period and the author feels that the results are better than with any other type of anastomosis except an accurate end-to-end. The Roux type of anastomosis of the jejunum produces a mechanical arrangement whereby the intestinal current is directed away from

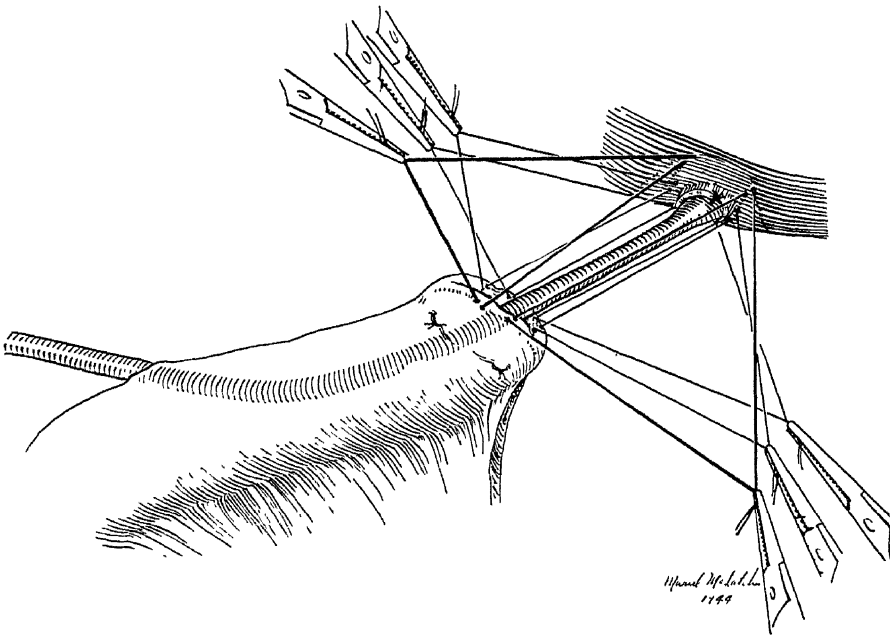


Fig. 4—Schematic representation of sutures of No. 30 cotton thread placed through the scar tissue in the liver sulcus and through the jejunum. The bell end of the catheter has been fastened to the stump of the hepatic duct by two plain catgut sutures. (Allen, A. W.: Ann. Surg. 121:412 (April) 1945.)

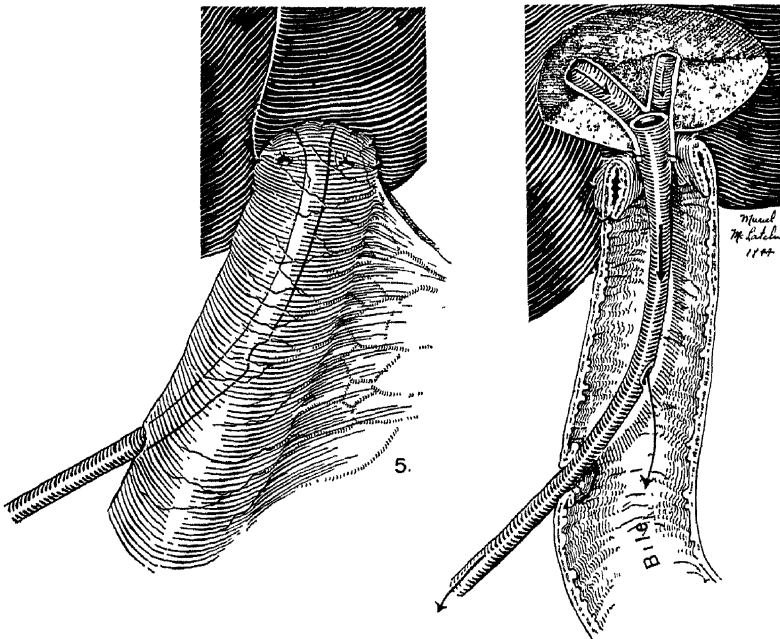


Fig. 5—Illustrates the appearance of the jejunum after the sutures to the liver surface have been tied.

Fig. 5a—Schematic representation of the approximate appearance of the tube *in situ*. (Allen, A. W.: Ann. Surg. 121:412 (April) 1945.)



the liver. Silk or cotton sutures securely hold the serosal surface of the jejunum to the serosal surface of the liver, thus assuring the best possible healing properties.

It is reported by Cole *et al.*<sup>2</sup> that a series of twenty-three cases of stricture or absence of the bile ducts (including two carcinomas of the common hepatic

removal of stones, even asymptomatic stones in patients below forty or forty-five years of age, prevention of operative trauma by adequate exposure, careful cystic duct dissection, individual ligation of cystic duct and cystic artery, and careful identification of structures before dividing them. Extreme care should be exercised in the performance of a chole-

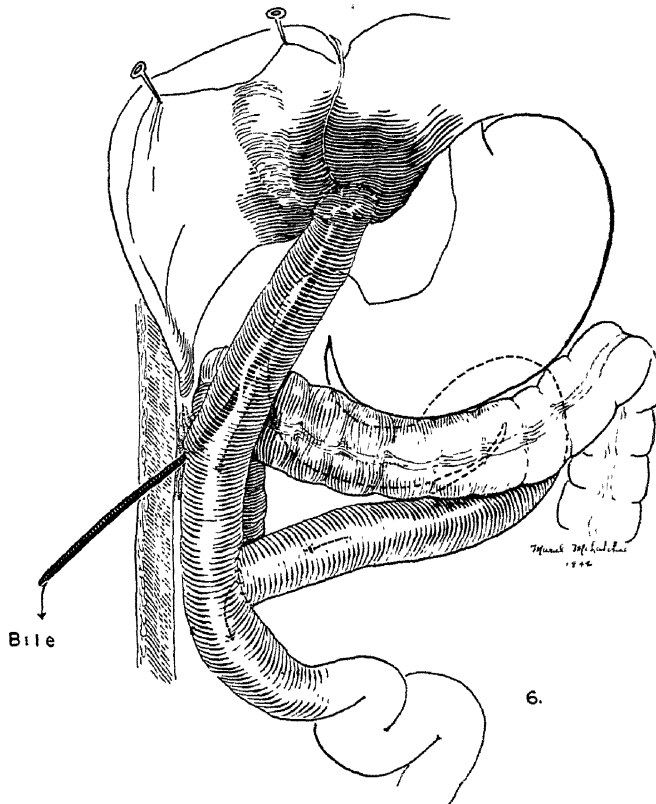


Fig. 6—Schematic representation of the finished operation. The proximal end of the jejunum has been reimplanted into the side of the distal end at a low level, the tube in the hepatic duct brought out through an omental tab, and a stab wound in the abdominal wall lateral to the incision. (Allen, A. W.: *Ann. Surg.* 121: 412 (April) 1945.)

duct) was encountered over a six-year period. In ten cases no ducts could be found except the stump at the hilum of the liver; in this group a vitallium tube was used for anastomosis. Causes of stricture of the common duct were tabulated.

In 76 per cent of the cases reported, operative trauma was probably the cause of the stricture. As a means of preventing strictures, the authors advise early

cholestomy, particular attention being paid to avoiding transverse incisions or tears and, if such should result, immediate repair of them.

The authors point out that the type of repair indicated in reconstruction of the bile ducts will depend upon the condition of the duct at operation. These are divided into:

1. Local stricture of the common duct, which is uncommon, being encountered

in only one of the twenty-three cases. In these cases the use of a vitallium tube may be satisfactory, but it was felt that a better procedure should be an end-to-end anastomosis over the arm of a "T"-tube inserted a distance of 2 or 3 cm. distal to the line of anastomosis. If a vitallium tube is used, the flange on the shaft, fixed by means of a nonabsorbable suture, seems indicated.

2. Stricture or absence of the terminal end of the common duct is also rare. The operation of choice in these cases is transplantation of the duct into the duodenum, using extreme care to approximate mucosa to mucosa over a rubber tube which will remain patent during the early period of postoperative edema. If stricture recurs or chills fol-

TABLE I

## CAUSES OF BENIGN STRICTURES OF COMMON BILE DUCT

1. Operative trauma:
  - (a) Excision, ligation, or incision.
  - (b) Clamped while controlling hemorrhage.
  - (c) Cystic-duct ligature too close.
  - (d) During gastrectomy.
  - (e) Following choledochostomy (rare).
2. Ulceration due to gallstones.
3. Inflammation:
  - (a) Related to cholangitis.
  - (b) Abscess about duct.
  - (c) Pylephlebitis.
4. Secondary to pancreatitis.
5. Tumors and multiple cysts.

(Cole, W. H., Ireneus, C., Jr. and Reynolds, J. T.: *Ann. Surg.* 122: 490 (Oct.) 1945.)

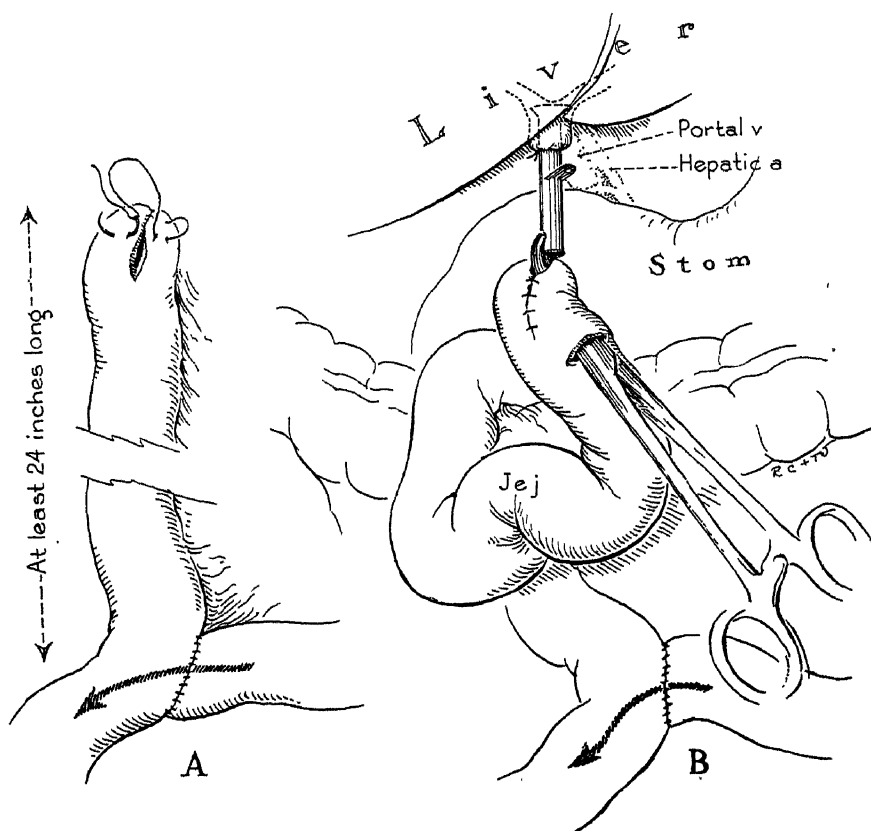


Fig. 7—After the ileum is severed and the proximal end sutured to the distal loop two to three feet from the point of severance, the distal end is closed with a continuous suture as shown in A. The end of the vitallium tube is inserted into the end of the intestine, aided by a hemostat threaded through a puncture wound two inches from the closed end as shown in B. (Cole, W. H., Ireneus, C., Jr. and Reynolds, J. T.: *Ann. Surg.* 122: 490 (Oct.) 1945.)

low this operation, anastomosis of an isolated arm of the jejunum may be advisable.

3. Absence or stricture of the common hepatic duct. These lesions are much more difficult to repair because anastomosis of the duct at the hilus of the liver cannot be readily achieved. The use of a vitallium tube, with the funnel

end projecting into the stump of the common hepatic duct at the hilus and the lower end protruding into the common duct, is the procedure of choice. A purse-string suture around the opening of the stump of the duct at the hilus serves to anchor the tube in the hilus. The end of the common duct is then inserted into the other end of the vital-

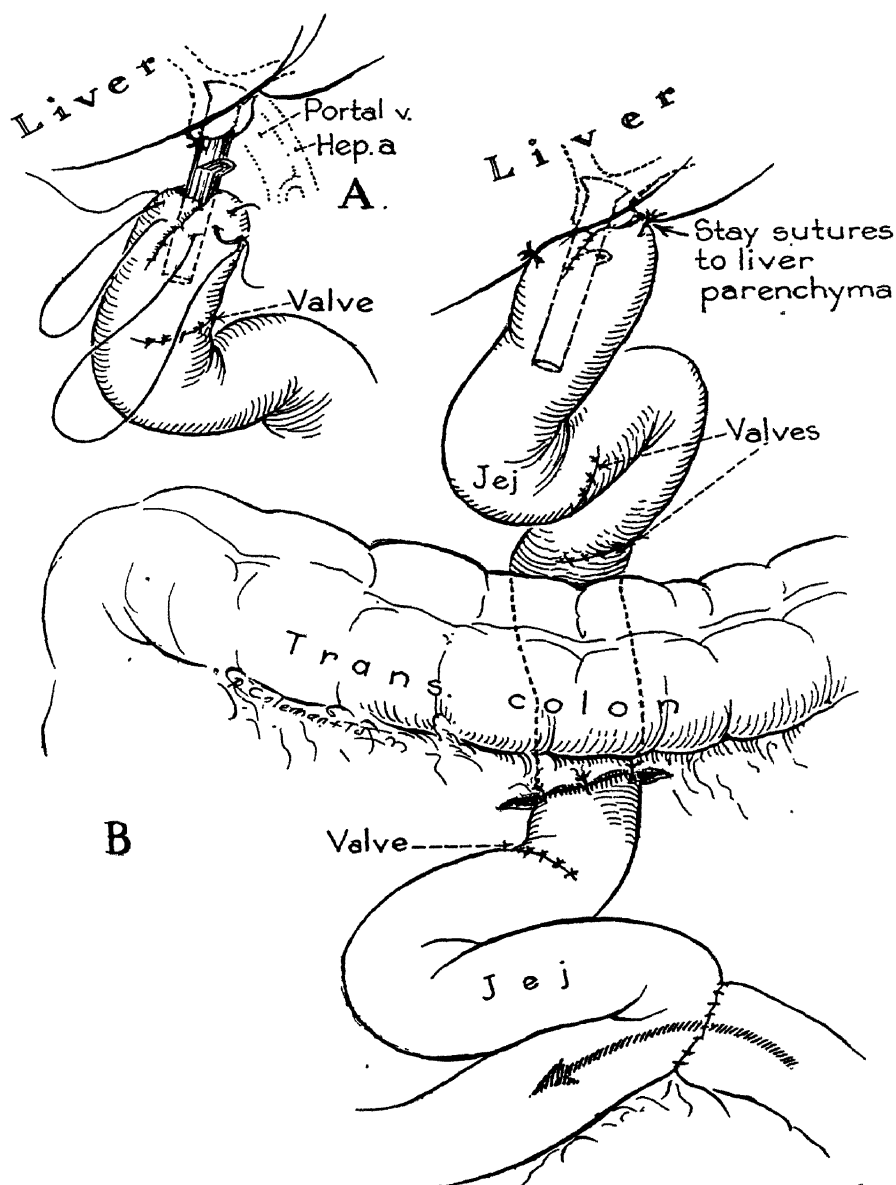


Fig. 8—The connection between intestine and distal end of the vitallium tube is made tighter by application of a purse-string suture of silk or cotton which is more easily applied before the tube is inserted. *B*, The end of the intestine is anchored against the liver by interrupted sutures, all of which should be inserted before any one is tied. (Cole, W. H., Ireneus, C., Jr. and Reynolds, J. T.: *Ann. Surg.* 122: 490 (Oct.) 1945.)

limum tube anchoring the duodenum to the hilus of the liver with the flange in the shaft protruding, if possible. If sufficient mobilization of the common duct cannot be obtained, it should be firmly anchored to surrounding tissue in order

question of repair becomes more difficult. Cholangitis is the pathological condition to be feared from anastomosis of intestines to the hilus of the liver. This is aggravated by the tendency for stricture to re-form and by the reflux of food

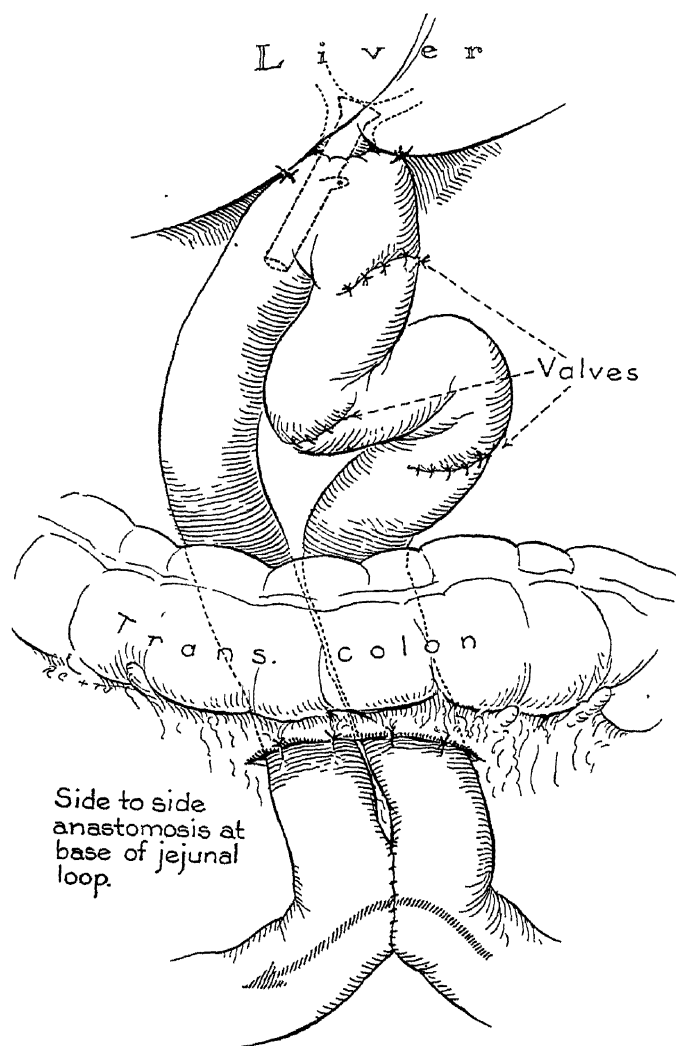


Fig. 9—An alternative and shorter method of constructing an outlet of bile to a defunctionalized portion of intestine is to insert the vitallium tube into a loop of jejunum. An enteroenterostomy should be performed eighteen to twenty-four inches from the point of insertion of the tube. However, in our experience, this method has ultimately been followed (as late as two years) by severe cholangitis presumably because of reflux of food and intestinal contents into the liver. Construction of valves as illustrated in Fig. 8 might minimize this tendency. (Cole, W. H., Ireneus, C., Jr. and Reynolds, J. T.: *Ann. Surg.* 122: 500 (Oct.) 1945.)

to prevent slipping from the end of the vitallium tube.

4. Absence of the common and common hepatic ducts. When no remnants of the common duct can be found, the

and intestinal secretions into the intra-hepatic ducts. In this type of case, the authors advocate anastomosis of the hilus stump to an arm of the jejunum after the Roux principle.

The jejunum is divided at a distance of at least one foot from the ligament of Treitz, the distal end is closed by inversion with a single suture of continuous catgut and the proximal end is anastomosed to the distal loop at least 2 feet from its end by an end-to-end anastomosis. The distal end may then

be inserted into the hilus of the liver and fixed by means of a purse-string suture, care being taken to avoid the portal vein and hepatic artery in placing this suture. The other end of the vitallium tube is brought through the distal end of the jejunum by means of a Pean clamp inserted through a counterincision in the

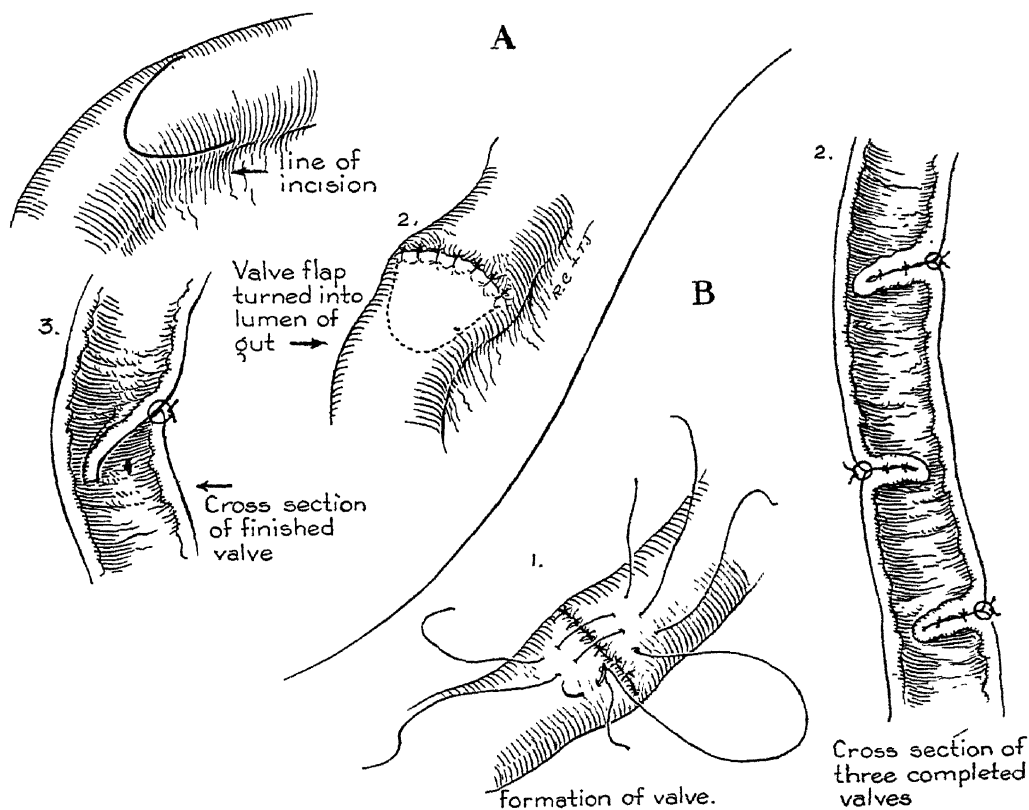


Fig. 10—In our experience, the construction of valves of one of the two types illustrated above eliminates reflux of food (as indicated by barium studies) and has minimized or eliminated the cholangitis. *A*, A valve may be constructed by outlining a flap of intestine and closing the defect after inverting the flap into the lumen. *B*, The creation of baffles by a double layer of sutures, infolding the wall of the intestine into the lumen, is probably as effective as *A* and is much more simply constructed. At least three of these folds should be made. No claim for originality is made for these valves, since similar ones have been reported for various purposes during the past several decades. (Cole, W. H., Ireneus, C., Jr. and Reynolds, J. T.: *Ann. Surg.* 122: 501 (Oct.) 1945.)

be brought up to the hilum of the liver in an anticolic or retrocolic position, depending upon existing tension. If the loop is brought through the mesocolon, it is essential to close this opening as in a gastroenterostomy. A funnel-shaped or "Y"-shaped vitallium tube is then

jejunum. The jejunum is then sutured to the undersurface of the liver by means of interrupted silk sutures. The opening made in the jejunum may be closed with interrupted sutures.

An alternate method is to attach a loop of jejunum to the hilus over a

TABLE II  
CONDENSED SUMMARY OF CASES OF STRICTURE OR ABSENCE OF COMMON DUCT TREATED BY IMPLANTATION OF A VITALLIUM TUBE

Case No.	Type of Obstruction	Type of Operation	Sex Age	G. B. Removed	Repair Operation	Convalescence	Remarks	Results
1		Duct at hilus of liver anas. to single arm (Roux 'Y') of jejunum (See Fig. 6)	F 23	Aug. 1941	May 1943	Uneventful	Feeling fine since operation except for epigastric pain. Had 3 chills since operation	Good to excellent
2			F 38	Dec. 1941	April 1943	Uneventful	No jaundice or acholic stools	Excellent
3			F 30	Feb. 1943	July 1944	Satisfactory	No complaints since last operation except one chill on 7-4-44. No jaundice	Excellent (except for draining sinus)
4			F 36	Jan. 1943	May 1943 (valves)	Uneventful	Since operation has gained 40 lbs. Had a few chills early but none during past 4 weeks. Still has draining sinus in wound (osteochochondritis?)	Excellent
5	No common or com. hep. duct found		F 39 D.S.	March 1943	April 20 and 26 1944	Stormy. Atelectasis and stubborn distention	Very few complaints. Is feeling better than previous to all operations, including the first	Clouded by development of Banti's syndrome
6		Duct at hilus of liver anas. to loop of jejunum (See Fig. 7)	F 34	Dec. 1941	June 1942	Uneventful	Large spleen found at reparative operation has increased in size (Banti's?). Stools normal color. Still jaundiced but no evidence of duct obstruction. Ascites	Excellent for 2 yrs. Now only fair
7			F 38	May 1935	5 ops. 1936 to 1943	Uneventful	Symptom-free for 2 yrs.; then chills and fever, without jaundice. Needs proximal loop severed	Excellent for 2 years; then chills, liver abscesses and death
8			F 54	April 1940	May '42 Jan. '40 (valve)	Biliary and internal fistula following 2nd operation, but healed in 2 weeks	Four anastomoses done over a rubber tube failed. Insertion vitallium tube into loop of jejunum afforded relief for 2 years, then developed multiple liver abscesses and died	Excellent since 2nd operation
9			F 56	May 1938	Feb. '42 Oct. '43	Uneventful	Symptoms recurred after 1st operation, because of reflux into ducts? Interruption of proximal loop to prevent reflux abolished symptoms	Excellent since 2nd operation (but developed arthritis and cardiac symptoms)
10			F 67	Aug. 1942	Jan. 1943	Postoperative wound infection. Hepatic insufficiency	Anastomosis with continuous loop of jejunum failed, but 2nd operation interrupting ascending loop abolished symptoms	Died
11	Defect of Ca in com. hep. duct. Distal com. duct found	Hilus duct anastomosed to com. duct	F 32	Jan. 1943	Oct. 1943	Uneventful	Anorexia, weakness, malaise increased, with reversal of blood protein. Primary cause of death hepatic insufficiency	Good to excellent
12			F 64	None Ca. C.D.	April 1944	Developed pyloric obstruction requiring a secondary operation	Has had an occasional mild chill. Also some epigastric pain	Good to excellent
13			F 34	Sept. 1943	Oct. 1943	Stormy. Wound infection and peritonitis	Had a resection of a Ca. of C.D. Repaired duct over a vitallium tube. Few mild chills. One attack of jaundice	Died
14	Prox. and distal duct found	Com. hep. duct to com. duct	F 38	May 1942	June 1942	Uneventful	Numerous large intra-abdominal abscesses were drained. At autopsy, many small liver abscesses found	Excellent after operation

(Cole, W. H., Ireneus, C., Jr. and Reynolds, J. T.: *Ann. Surg.* 122: 507 (Oct.) 1945.)

vitallium tube and establish an entero-enterostomy between the limbs 18 to 24 inches below the anastomosis.

This method was followed by cholangitis as late as two years after the operation. Construction of valves may minimize the tendency for intestinal contents to enter the liver. An analysis of the fourteen cases is well tabulated. These cases are all presented in detail. While the authors felt that obstruction was

The clinical aspects of traumatic stricture of the hepatic duct following cholecystectomy were discussed by Colp<sup>3</sup> and five cases, in which the operation of hepatoduodenal intubation with hepatoduodenostomy was performed, is presented. It is pointed out that after cholecystectomy the bile may drain externally for several weeks or months and when this diminishes jaundice of the obstructive type occurred. Occasionally, there

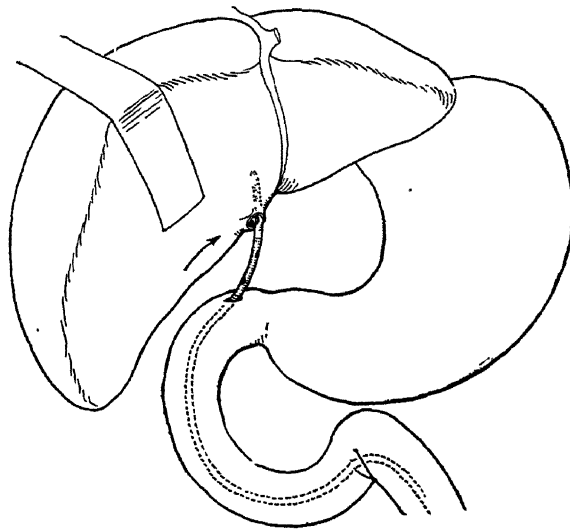


Fig. 11—Case 1. Catheter entering left hepatic duct with side hole to drain the right. (Colp, R.: *Surg., Gynec. & Obst.* 80: 190 (Feb.) 1945.)

prevented by the use of a tube, they did not find that it prevented chills and fever characteristic of cholangitis, unless the reflux of food was directed away by the operative procedure. In the fourteen cases, there was an operative mortality of 14.3 per cent. One of these cases was considered an extremely poor risk, but operation offered the only chance of cure. It was suggested that tantalum may be better than vitallium because it is more pliable, easily bent, and cut to any desired length; however, a flange and funnel would be essential in order to maintain the tube in its proper position.

is a painless type of jaundice of increasing intensity developing months after removal of the gallbladder. Intermittent fever and chills are not uncommon due to an ascending cholangitis, a cirrhosis, or multiple liver abscess. Nutritional disturbances are also present. The usual physical findings are anemia, dehydration, weight loss, jaundice, and an upper abdominal scar, either draining bile or healed. The liver is usually enlarged, palpable, and tender. Correction of the dehydration and electrolytic imbalance, restoration of liver by a high protein, high carbohydrate diet, supplemented by plasma or amigen, is essential. The use

of vitamin K bile salts and transfusion has also been important in the preparation of these patients for operation. For these operations, continuous spinal is the anesthetic of choice. In cases where an end-to-end anastomosis cannot be performed, the authors suggest placing a fenestrated tube into one of the hepatic ducts, then passing the distal end into an opening made into the opposing duodenal wall directly toward the jejunum. The tube may also be passed through the pylorus and brought out of the an-

However, cases have been reported in which the tube has remained in place as long as eight years. The possibility of obstruction, due to inspissation and incrustation with bile salt, is ever present. The author did not feel that sufficient time has elapsed to demonstrate the advantages of the vitallium tube over the rubber tube. It was pointed out that the danger of an ascending cholangitis following a reconstruction of this type, with the loss of sphincter mechanism and reflux of the intestinal contents into the

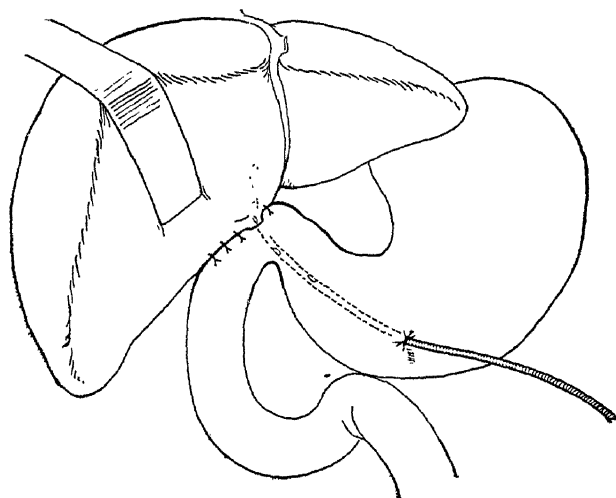


Fig. 12—Case 2.

(Colp, R.: *Surg., Gynec. & Obst.* 80: 190 (Feb.) 1945.)

terior wall of the stomach similar to a gastrostomy. Interrupted mattress sutures of linen approximate the serosa of the duodenum to Glisson's capsule of the liver in the region of the hepatoduodenostomy. It is necessary to place posterior and lateral sutures before tying the anterior group. In five cases reported, a complementary jejunostomy for alimentation was performed about 18 inches from the duodenojejunal angle, the tube being brought out through a left lateral stab incision. It was pointed out that the rubber tube is usually passed within a period of three to twelve weeks.

bile duct associated with partial obstructive phenomena, was common. In the five cases which the author reported in some detail, one remained well for four years, one fifteen months, one four months, and in the other two cases Charcot's fever had occurred more or less frequently for three years in one case and eighteen months in the other. A recurrent stricture was considered the cause of this complication. In one case, a subtotal gastrectomy was performed in order to divert the stomach contents from the duodenobiliary anastomosis without relief. Detailed case histories



and operative findings on the five cases, all of which survived operation, are reported.

A case of stricture of the common bile duct successfully treated by the use of a vitallium tube was reported by Saint.<sup>4</sup> The patient made a satisfactory recovery. She remained well for nineteen months after operation. Results from this method of anastomosis have been sufficiently satisfactory to warrant further use of the tube in selective cases.

McGowan<sup>5</sup> presented a case in which it was thought that a stricture of the ampulla of Vater produced a regurgitation of bile into the pancreatic duct and pancreatitis. Pancreatitis then produced obstruction to the common bile duct and gallbladder resulting in cholangitis and cholecystitis. It is pointed out that chills and fever, which are common symptoms of cholangitis, may be confused with malaria in malaria areas. In this case the gallbladder was removed and the common duct drained by means of a "T"-tube, which the author considers the best treatment for pancreatitis. The "T"-tube should remain in place until all evidence of pancreatitis and cholangitis has disappeared. Spasm of the duodenum, which is usually an important factor in postcholecystectomy syndrome, was of no importance in this particular case because the common bile duct and the pancreatic duct entered the duodenal wall through separate tunnels opening into the ampulla of Vater inside of the duodenum. It was suggested that the "T"-tube should be removed only (a) when the resting intrabiliary pressure is 30 mm. or less of water; (b) the perfusion pain level is 500 mm. or more; (c) roentgenologic studies of the common duct show the absence of any obstruction to the flow of bile into the duodenum; (d) the clinical test by clamping off the "T"-tube for a period of three weeks.

## Carcinoma

Brunschwig and Bigelow<sup>6</sup> point out that simple exploratory celiotomy, with or without attempts to drain the biliary tract, has led to poor palliative relief in the majority of cases. In view of this fact, they subjected seven patients with advanced carcinoma involving the extrahepatic bile passages and the gallbladder to radical resection of these ducts and the gallbladder, sometimes excising involved liver tissue, and, in one instance, a portion of the head of the pancreas. These cases were summarized as follows:

(Case 1.) A male, aged 67, carcinoma involving extrahepatic bile ducts, gallbladder, its liver bed, and the upper right lateral portion of head of pancreas. Survived operation for one year. Icterus completely cleared; return to full-time normal activity for several months; gain in weight. Second operation performed when icterus recurred eleven months after first operation. Vitallium tube inserted into dense mass of recurrent carcinoma in porta, but condition did not improve, and the patient died one month later. No necropsy.

(Case 2.) A 63-year-old male with carcinoma of the cystic duct and invasion of the gallbladder, hepatic duct, and common bile duct. Death twenty-two days after operation. Necropsy showed that the hepatic artery had been resected with the tumor and infarction of the liver occurred.

(Case 3.) A male, aged 59, carcinoma of extrahepatic bile duct with the invasion of the gallbladder. Died six days after operation. During the operation the portal vein had been opened and ligation unnecessary, a segment of hepatic artery was insected with the tumor. Necropsy revealed extensive septic infarction of the liver.

(Case 4.) A female, aged 56, carcinoma of the extrahepatic bile ducts with invasion of the gallbladder and metastatic nodule in the liver adjacent to gallbladder. Living five months after excision. Icterus completely cleared. Moderately comfortable but gradually losing weight.

(Case 5.) Female, aged 60, carcinoma of extrahepatic bile ducts with involvement of gallbladder. Survived radical excision three months. Icterus reduced but not relieved. Necropsy not obtained.



Fig. 13—1, Common bile duct; 2, hepatic duct; 3, point at which the lower end of the common bile duct begins to tunnel the musculature of the duodenal wall; 4, pancreatic duct; 5, ampulla of Vater; 6, duodenum; 7, duodenal tube passed through the nose; 8, "T"-tube in common duct. *A*, This shows a moderate degree of spasm of the duodenum, the intramural portion of the common bile duct between 3 and 5 is definitely narrowed. The intramural portion of the pancreatic duct between 4 and 5 shows a narrowing for a shorter distance than that of the common bile duct, since it tunnels the duodenum at a right angle rather than obliquely. The fact that the media regurgi-

tated from the common bile duct to the pancreatic duct shows that there is some obstruction at the ampulla of Vater. This could be in the nature of a fibrosis. A spastic duodenum would add to this narrowing, since it would cause the folds of the duodenum to overlap each other. The muscle spasm of the duodenal wall, however, would not directly encourage regurgitation into the pancreatic duct of the bile in this case, since the pancreatic duct tunnels the duodenal wall independently of the bile duct. Note also that there is no regurgitation of barium into the stomach. On the other hand, the barium is being carried at regular intervals downward into the jejunum, a condition which exists where there is not much spasm of the duodenum and probably not much irritability of the biliary tract from infection or otherwise. *B*, This was taken ten minutes after subcutaneous administration of 10 mg. ( $\frac{1}{6}$  grain) of morphine. The duodenum is now in complete spasm. The lower end of the common bile duct is completely shut off as a result of this. There is regurgitation of barium through the pylorus into the stomach, as indicated by the rugal markings above 7. This indicates a relaxed pylorus. The condition in which a spasm of the second portion of the duodenum is associated with a reciprocal relaxation of the pylorus occurs very frequently. This is the beginning of the vomit reflex; it is associated with antiperistalsis of the duodenum. *C*, This was taken two minutes after inhalation of amyl nitrate. Note the complete relaxation of the duodenum and the freedom with which the media runs from the common duct into the duodenum. Note that there is some narrowing at the ampulla of Vater other than spasm, probably a fibrosis as a result of a previous duodenitis. Note that there is no reflux of barium into the stomach. The pyloric tone has recovered. Peristalsis now is in a downward direction toward the jejunum. (McGowen, J. M.: *Surgery* 18: 473 (Oct.) 1945.)



(Case 6.) Female, aged 72, carcinoma of extrahepatic bile duct with involvement of gallbladder. Survived radical excision five months. Icterus completely relieved. Moderate comfort during period of survival. No necropsy.

(Case 7.) Female, aged 49, carcinoma of lower common hepatic duct and upper common

excess to porta hepatis; (3) dissection of gallbladder from liver bed and wedge excision of liver with gallbladder when necessary. Hemorrhage controlled by large mattress sutures; (4) hemostat to gallbladder and traction upward to ele-

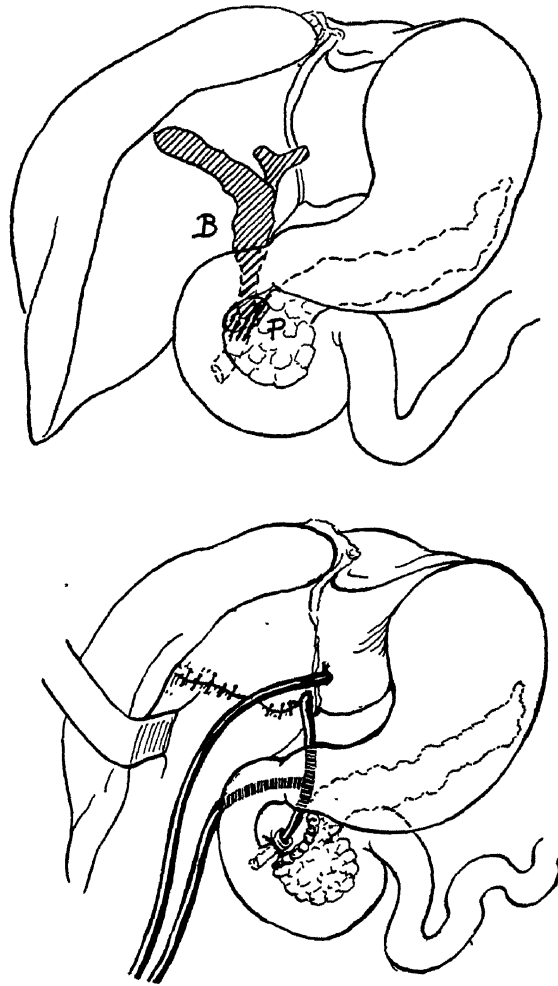


Fig. 14—Case 1. S. P. (26486). A, Findings at operation—carcinoma (shaded area) involving practically entire extrahepatic biliary tract with invasion of head of pancreas. B, Termination of operation after excision of extrahepatic biliary tract, gallbladder, liver immediately surrounding it and portion of head of pancreas. "T"-tube in right hepatic duct sinus and stump of common duct; urethral catheter in left hepatic duct stump. Survival, one year (see text). (Brunschwig, A. and Bigelow, R. R.: *Ann. Surg.* 122: 522 (Oct.) 1945.)

bile duct with invasion of gallbladder. Died thirteen days after operation. Bile peritonitis at necropsy.

Under continuous spinal anesthesia, the procedure followed was: (1) A high or reverse "L" incision; (2) aspiration of gallbladder is necessary to facilitate

vate the mass in the porta hepatis; (5) isolation of lower segment of common duct behind duodenum after mobilization of duodenum and head of pancreas by incision of parietal peritoneum along with greater curvature of the duodenum; (6) transection of common bile duct

behind duodenum and incisions into head of pancreas to mobilize the portion invaded by carcinoma, if this was present; (7) applications of hemostats to upper segment of transected bile duct to sections carried up to free involved extrahepatic bile duct from surrounding areolar tissue. This is dangerous because the hepatic artery and portal vein may be opened during liberation; (8) after liberation of carcinomatous ducts and attached gallbladder, the right and left hepatic ducts are transected at or beyond their emergence from the liver and the specimen removed; (9) in these cases, the duodenum could not be mobilized sufficiently to reach the liver; therefore, one of three procedures was followed: (a) Two "T"-tubes were inserted, one in the left and one in the right hepatic duct stumps, and the lower arms inserted together to the lower stump of the hepatic duct; (b) a "T"-tube inserted between the right hepatic duct and common duct stump and a urethral catheter inserted into the left hepatic duct; (c) the left hepatic duct ligated, "T"-tube inserted between the right hepatic and common bile ducts. Soft rubber drains into the right kidney fossa and abdominal wall closed. It was pointed out that injury to the portal vein and hepatic artery constitutes the greatest hazard of this procedure. Of the four who survived operation, one lived for a period of a year, two lived five months, and one, three months. It was not thought that the survival had in any way been lengthened; however, the icterus was ameliorated. The frequency with which jaundice developed late in the course of carcinoma of the bile ducts adds greatly to the difficulty of an early diagnosis. The principal symptomatology was icterus, pain, dyspepsia, and marked weight loss, which varied from two weeks' to six months' duration. The greatest weight

loss in the cases reported was 70 pounds within an eight-month period.

Irwin and Morison<sup>7</sup> report a case of a male, aged thirty, upon whom an appendectomy was performed, through a gridiron incision, due to pain in the upper abdomen.

Pain recurred in fifteen months, associated with jaundice. The patient was again operated upon and the gallbladder was distended and liver was tense. A tumor, about the size of a fist, was found in the region of the head of the pancreas. This was aspirated and found to contain bile; the cyst was opened and gallstones removed; a tube sewed into the common duct and a cholecystogastrostomy performed. The patient died.

At autopsy, the cystic and hepatic ducts were found to be normal in size; the common duct dilated, but a probe could not be passed into the duodenum. Upon histological examination, a squamous-cell carcinoma, believed to have originated in the common duct, was found.

### Fistula

An unusual type of combined internal and external biliary fistula was reported by Gray and Sharpe.<sup>8</sup> The external drainage of bile was easily recognized, but the concomitant cholecystogastroduodenal fistula was not discovered until operation. Partial gastrectomy, partial duodenectomy, and cholecystectomy were performed with a good result. The common bile duct was explored and drained. It is stated that relatively few cases of internal fistula, caused by stone erosion, are recorded in the literature. Treatment of internal biliary fistulae depends entirely on the findings in each case. Stones should be removed if possible, fistula should be excised and the opening in the stomach or intestines should be closed. The gallbladder should be removed and the common duct should be

drained if there is any doubt as to its patency.

The case reported was a fifty-eight-year-old male suffering from an external biliary fistula of ten months' duration, and pain and jaundice of ten days' duration. Ten months previously he had been operated upon for cholecystolithiasis. The gallbladder at that time showed an abscess in the wall with many stones. Bile drained profusely for the first two weeks after this operation. Following this, the biliary fistula persisted and he would occasionally discharge a stone from the tract. Examination showed icterus of a mild degree, a poorly healed scar in the upper part of the right rectus with two granulating regions which gave the appearance of a recently healed sinus. No mass or drainage was evident at the time of admission.

At operation, a large number of upper abdominal adhesions were encountered. The gallbladder was chronically inflamed and contained several small stones. The fundus of the gallbladder was densely adherent to the duodenum, and the sinus tract seemed to arise from this region. The common bile duct was about three times its normal size and contained normal bile as well as sand and puttylike material. Scoops could be passed into the duodenum, a "T"-tube was inserted into the bile duct, and the gallbladder was removed from below. In the region of the pylorus, the fundus of the gallbladder was attached and a very hard irregular mass about 3 cm. in diameter was felt. Due to the possibility of malignancy and further mechanical obstruction, a partial gastric resection with removal of a small rim of duodenum was performed. A posterior Polya anastomosis was done. Patient made an uneventful convalescence. A pathological examination showed an inflamed cholecystogastroduodenal fistula, 3.5 cm. long,

extending obliquely and distally from the serosal opening situated 2 cm. proximal to the pyloric ring on the anterior wall of the stomach to a mucosal opening in the duodenum 1 cm. distal to the pyloric ring. The fistula contained multiple stones, the largest of which was 1.5 cm. in diameter.

### Rupture of Common Duct

According to Schena,<sup>9</sup> only eight cases of rupture of the scar in the common duct after draining for infection have been reported in the literature. He reports the case of a forty-eight-year-old woman who had a gallbladder removed and the common duct drained for stones one year before the second operation. At this operation a residual stone was removed from the common duct due to recurrence of symptoms and drainage was established by a Kehr tube. This tube was retained for thirteen and one-half months. Six months after its removal, signs of peritonitis developed and operation showed infected bile flowing into the peritoneal cavity from a rupture of the operative opening in the common duct. The pus was encysted, partly because of the presence of adhesions from the former operation, and the patient recovered.

Factors concerned with the rupture of a choledochostomy scar are increased pressure within the duct and infection. These soften the cicatricial granulations and make them friable. Digestion of the tissues from pancreatic reflux may also be a factor. Excessive denudation of the common duct during the operation, which deprives the wall of its vessels, may lead to mortification. This may occur when it is difficult to free the common duct from dense inflammatory infiltration, and it is particularly apt to occur when a second operation has to be performed as in this case.

### Roentgenograms

Sahler and Hampton<sup>10</sup> point out that common duct stones can often be demonstrated on plain abdominal roentgenograms or spot roentgenograms of the bile duct area. Calcification at the region of the gallbladder or common duct, the demonstration of calcium bile milk, or jaundice should make one suspicious. It is not generally appreciated that plain roentgenograms may visualize common duct stones. This is probably due to two factors, the relative infrequency of common duct stones, and the difficulty in demonstrating their location accurately.

A diagnosis of common duct stones from plain roentgenograms is dependent upon the presence of sufficient calcification to give a positive shadow. About two cases per year, in which common duct stones can be demonstrated, are encountered at the Massachusetts General Hospital. Without contrast media, it is difficult to establish a definite diagnosis due to the impossibility of accurately locating the shadow. The differentiation of common duct stones from renal or cystic stones is the first problem which must be solved. Since a stone in the cystic duct may lead to hydrops of the gallbladder and one in the common duct would not, a mass in the gallbladder region associated with calculus is indicative of a cystic duct stone. Cystic duct stones, however, do not always produce hydrops. A stone lying in the region of the duodenum or duodenal loop demonstrated in anteroposterior film justifies a diagnosis of common duct stones. Rarely a dye study of the gallbladder will show the power of concentrating the dye and subsequent contraction following a fatty meal in the presence of gallbladder disease. In such an instance, the bile duct would probably be outlined by the dye and stones could still be accurately located.

**Cholangiograms** — In a series of 276 cases, Mentzer<sup>11</sup> has performed an immediate cholangiogram. An aqueous solution of iodine (hippuran) in quantities from 8 to 15 cm. is injected through a 24- or 26-gauge needle inserted obliquely through the wall of the common duct. Since the solution is aqueous and mixes with bile, withdrawal of bile was not necessary. The injection was made after exposure of the common duct. Before the patient was draped for operation, a cassette with a 14 by 17 film was inserted under the patient's back. Immediately after the injection, an x-ray is taken at a focal distance of 18 inches, the focal site being previously marked by a dot of merthiolate on a sterile towel. The gallbladder was removed while the x-ray film was being developed. If the duct was normal, the dye was found to enter the duodenum without evidence of obstruction or dilatation of the choledochus. In cases of dyskinesia, a subsequent film taken fifteen or twenty minutes later showed the sphincter of Oddi relaxed and the solution in the intestinal tract. The author felt that the simplicity of the method warrants widespread use by the general surgeon.

Mirizzi<sup>12</sup> reports that among 1278 cases of acute pancreatitis, there was disease of the biliary tract in 894, or 70 per cent. This relationship is brought about by a dystonia of the sphincter of Oddi, which results in the reflux of bile into the duct of Wirsung and, conversely, of pancreatic secretion into the biliary tract.

Biliary lithiasis is a prominent factor in the causation of acute and chronic pancreatitis. Conversely, the reflux of pancreatic secretion into the biliary tract is a factor in the etiology of such diseases of the biliary tract as perforation of the gallbladder, exfoliative cholecys-

titis, and biliary peritonitis. It is not the presence of the pancreatic secretion in the bile passage itself that causes the trouble, but the fact that it changes the reaction of the bile from acid to alkaline and thus makes it a good medium for activating trypsin to the point where it digests the tissues. It was pointed out

grams taken the following day showed complete relaxation and normal passage of bile from the common duct.

A mistake is often made in cholangiography. Often a closed infundibuliform termination of the common duct is found, which apparently would allow no passage of bile into the duodenum. Upon



Fig. 15—Photograph of the surgical specimen, showing the internal surface of the resected portion of the stomach with large gallstone lodged in the wall at the gastroduodenal juncture. (Gray, H. K. and Sharpe, W. S.: *Ann. Surg.* 122: 48 (July) 1945.)

that this flow could be demonstrated by operative cholangiography. Various cases of disease of the biliary tract and pancreas are described and illustrated.

Two cases of what was called obstructive odditis are described by Negri.<sup>13</sup> Observation was kept up for fifteen to twenty minutes and still the cholangiograms showed obstruction. Cholangio-

further examination, it is often shown that a contraction of the sphincter of Oddi may be the cause and when the sphincter relaxes, the passage of bile becomes normal. A single cholangiogram cannot determine whether a true obstruction exists at the end of the common duct, or whether the apparent obstruction is functional because no time

can be set for normal continuance of the contraction.

Cholangiograms showing partial contraction, which simulates a stricture of the sphincter, but disappears with complete relaxation, are illustrated.

Bengolea is given credit for the observation that disclosed these facts which were previously unknown.

### Identification of Common Duct

As a means of constantly identifying the condition of the common duct and its point of entrance in the duodenum, Lahey<sup>14</sup> advocates the insertion of a "T"-tube in the common duct. This procedure is advocated only in the difficult cases due to adherence to the pancreas or the lateral wall of the duodenum with shortening of the duodenum where excision of the duodenal ulcer is anticipated. By the use of this method, they have increased the number of cases in which the ulcer could be resected while doing a partial gastrectomy. In cases where it is doubtful whether the ulcer-bearing portion of the duodenum can be safely removed, a two-stage procedure is advocated. This consists of

anterior gastroenterostomy, with removal of the omentum or the Finsterer resection by exclusion type of operation, with the understanding that the ulcer-bearing portion of the duodenum and the pylorus will be removed at a later date when the ulcer has healed and the induration disappeared.

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## GALLBLADDER

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### Etiology

**Rôle of Infection**—Experimental studies as to the etiology of cholecystitis are reported by Rehfuß and Nelson.<sup>1</sup> They continued experiments over a fifteen-year period, using over 100 antigens obtained from patients. In the first series, using sixteen strains of seven different types of organisms, eighty-eight rabbits were injected. Some degree of

chronic cholecystitis was produced, with organisms from each group. The most effective being a nonhemolytic streptococcus isolated from the bowel of a patient suffering from chronic cholecystitis and colitis. Inoculation of sixty-six of the eighty-eight rabbits with non-hemolytic streptococcus caused gallbladder disease in thirteen (20 per cent). A later study, using various bacterial



organisms in 129 rabbits, resulted in 25 diseased gallbladders (approximately 20 per cent).

An attempt was made to regulate the dosage so that it would simulate focal infection in man. This was done by small intravenous injections of 0.02 to 0.05 cc. of an eighteen- to twenty-four-hour culture twice a week. The viable strain of *Streptococcus nonhaemolyticus* was injected into 166 animals until a chronic illness was evident. Eighty-four diseased gallbladders were thus obtained (51 per cent). These animals were divided into three groups: Control, vaccine-treated, and filtrate-treated. The selections were based on similarity of response to the culture inoculation, the temperature and weight changes, and the presence of joint disease.

Another experiment was continued on 244 animals. By comparing the infective phase, the animals were grouped into 74 control, 75 vaccine-treated, and 75 filtrate-treated. Thirty-one animals which died or were killed, when death was imminent, were excluded. Gallbladder lesions were noted in 153 of these animals or 68.3 per cent. Only 37 or 16.5 per cent had an active infection, and the *Streptococcus nonhaemolyticus* was recovered from the bile in only 20 or 8.9 per cent. It was apparent that both gallbladder lesions and coexistent kidney and joint lesions were often sterile.

The gross findings at necropsy were classified as: (a) Doubtful; (b) plus 1; (c) plus 2; (d) plus 3. Any difference observed was in favor of the animals who received vaccine treatment. Of the control group, 64.7 per cent were positive and 4.1 per cent doubtful. Of the vaccine group, 44 per cent were positive and 20 per cent were doubtful. Of the filtrate group, 64 per cent were positive and 8 per cent doubtful. The observa-

tion of doubtful lesions at the termination of treatment may signify a state of involution or the persistence of a low grade infection. In view of the small percentage of doubtful gallbladder lesions among the controls, it was felt that the evidence favors the assumption that the doubtful lesions were undergoing involution.

On the whole, the general survey showed that gallbladder damage was constant in all three groups, indicating that the viable organism was responsible for the changes. No gross or microscopic change was found in nine normal animals selected from the stock.

**Foreign Bodies**—Heatley and Bascomb<sup>2</sup> report the case of a sixty-one-year-old woman complaining of pain in the left hypochondrium, loss of appetite, and a loss of 25 to 30 pounds within one year. She suffered from an acute episode of right subcostal pain one year prior to her admission. This subsided spontaneously. Following the acute episode, there was soreness and tenderness in the upper right abdomen with intolerance to fatty foods and increasing episodes of epigastric distress. An x-ray examination revealed two metallic bodies in the gallbladder. Operation disclosed a normal liver with dense fibrotic adhesions anchoring the gallbladder firmly to its bed. This was thought to be due to metallic objects perforating the gallbladder into the liver. Recovery followed operation. The patient gave a history of swallowing a closed safety pin twenty years before. She had been a dressmaker and of necessity had many pins in her mouth during her lifetime. The authors were not certain whether the pins removed were the shafts of a safety pin or whether they were straight pins swallowed at different times.

**Gallstones**—As a result of an exhausting study on the preponderance of

gallstones in women, Robertson<sup>3</sup> comes to these conclusions:

1. It is a well-established fact that women are more liable to have gallstones than men.
2. Gallstones occur almost exclusively in both men and women during the time of life when sex functions are active.
3. Any explanation of why gallstones are formed must be in harmony with these two facts.
4. The production of gallstones takes place as a rule only in the gallbladder.
5. Neither abnormal stasis of bile nor bacterial infection nor other disease is responsible for cholelithiasis.
6. The clinical symptoms and signs produced by the presence of gallstones have no relation to the etiologic factors of their formation and often occur many years after the gallstones are produced. Most gallstones at the time of their inception, and often for many years afterwards, are relatively silent.
7. Cholesterol, the chief constituent of gallstones, together with bile pigment and calcium, is normally held in a state of colloidal dispersion by bile acids and their salts.
8. A relative excess of cholesterol or decrease of bile salts may lead to the precipitation of the colloiddally suspended elements of the bile.
9. A binding substance, most likely an excess of changed mucin or other related nucleoalbumin, serves to mold and preserve the precipitated substances in the form of calculi. There is little evidence that mucin or nucleoalbumin can act as a precipitating medium.
10. In order that gallstones may be formed, there must be simultaneous disturbances in both the absorptive and secretory function of the mucosa of the gallbladder and its walls.
11. During the time of active sex life of both men and women, neurogenic hormonally controlled disturbances, both in the central and the vegetative nervous systems, are frequent and occasionally cause profound functional changes, particularly in the vascular system, smooth muscles, and secretions. These influences are more pronounced in women than in men, but in both they at times cause serious alterations in the absorptive and secretory functions of the gallbladder, produce a changed mucin or mucoid substance in the bile, and disturb the normal balance or ratio of cholesterol and bile salts.
12. Gallstones are primarily the result of functional disturbances, which are effective only on infrequent occasions and are active

over comparatively short periods of time, although repetitions of their effects, as well as complications due to obstructive phenomena or secondary infections, may at times occur.

13. Functional upsets, primarily, but not always, responsible for gallstones, should be distinguished from secondary or subsequent pathological conditions, which often cause clearly recognizable and occasionally serious clinical diseases.

14. More study is indicated in order that the psychic and other neurogenic disturbances which produce gallstones may be recognized while in action, and thus afford a sound basis for prophylaxis and treatment.

Four cases of sickle cell anemia in which gallstones were demonstrated roentgenologically are reported by Weens.<sup>4</sup> A record of cholelithiasis was found in twelve of forty-four autopsy cases of a sickle cell anemia, all twelve being less than forty years of age.

Sickle cell anemia gains relative importance as an etiological factor in the development of gallstones in the colored race, as there is a lower incidence of cholelithiasis in the colored race than in the white. The basis of biliary colic cannot solely explain the crisis of sickle cell anemia. The abdominal symptoms in some patients are due to cholelithiasis and associated gallbladder disease. It is important to recognize sickle cell anemia as a cause of acute and chronic abdominal symptoms so that unnecessary operations may be avoided. When sickle cell anemia and biliary calculi are both present, careful evaluation of all clinical symptoms is required before operation is advised. When cholelithiasis is present, in a young negro particularly, it is essential to search for the presence of sickle cell anemia.

In a discussion of the causes of abdominal pain in children, from a surgical standpoint, Strauss<sup>5</sup> points out that gallbladder disease, gallstones, and obstruction of the common duct are much more common in young children than one

realizes. There is extreme difficulty in differentiating acute cholecystitis from a high appendix with a nonrotated cecum. If gallbladder disease is suspected and the condition persists, exploration is indicated. A cholecystectomy is the operation of choice if stones are present. In the more serious cases, cholecystostomy with removal of the stones may be the operation of choice. Mention was made of an eleven-year-old boy from whom a stone was removed from the ampulla of Vater. There were no stones in the gallbladder. This child had suffered from repeated attacks of abdominal pain and also suffered from diabetes mellitus. The diabetes subsided following removal of the stone from the common duct.

A white female patient, aged thirty-seven, suffering from cholecystitis, is reported by Schenken and Coleman.<sup>6</sup> Following a cholecystectomy, the gallbladder was found to contain 36,329 stones.

### Pathology

In an attempt to determine the significance of leukocytes in the wall of the gallbladder, McKibbin and McDonald<sup>7</sup> studied twenty-five thin-walled noncalcareous gallbladders which had been removed surgically. These were translucent when held to the light and held no gross evidence of inflammation. A comparative study was carried out on twenty-five so-called strawberry gallbladders and twenty-five gallbladders that contained stones in order to eliminate the effect of iodized dye. An interval of at least twenty days was chosen between the administration of the dye and the study. Ten gallbladders from dogs were also studied. Ten gallbladders from fetuses, aged three to five months, were studied.

The outstanding finding was not only the consistent presence of polymorphonuclear leukocytes in the thin-walled noncalcareous gallbladders, but their

presence in similar numbers in all of the gallbladders examined except the nonfunctioning fetal gallbladders. The authors felt that the polymorphonuclear leukocytes were serving a metabolic function rather than an inflammatory function when they were found unassociated with other kinds of inflammation.

**Congenital Absence** — Dixon and Lichtman<sup>8</sup> were able to obtain satisfactory reports in thirty cases of congenital absence of the gallbladder before 1900 and fifty since that time. To these they added ten cases observed at the Mayo Clinic. The theories advanced to explain the congenital absence of the gallbladder are: (1) An anomaly due to failure of the gallbladder bud to develop from the hepatic diverticulum. This would also result in absence of the cystic duct; (2) the anomaly is due to failure of the gallbladder bud to resolve from its solid embryonic stage. The presence of a solid cord residue would favor this theory.

The cases reported before 1900 were often inadequate. In twenty-four of the thirty cases, the anomaly was found at necropsy; in two at operation and confirmed at necropsy; while in four there was no mention of how the anomaly was discovered. In the five cases with adequate history, symptoms suggestive of cholelithiasis were present. Jaundice was present in six cases. The common duct was dilated in five of the ten cases, the cystic duct was present in four cases, stones were present in two, twelve were female and ten male. Eight infants were included and ten patients were more than forty-five years of age.

To the fifty cases which they considered adequate since 1900, they add ten cases, making a total of sixty. In twenty-six of these cases, the anomaly was found at necropsy and in the remaining thirty-four it was found at operation. In

six of the thirty-four cases, the condition was confirmed at necropsy. In twenty-four of the sixty cases, the anomaly was found in the course of operation for suspected cholecystic disease. The average age of these patients was 46.7 years. Forty-two of the patients were more than forty-five years of age and four less than one year. There were thirty-six males and twenty-three females; in one the sex was not mentioned. Symptoms suggestive of cholecystic disease were present in thirty-five cases. In eight patients the pain extended to the left side of the thorax into the scapula. In thirteen the symptoms were not referable to the gallbladder and in twelve the symptoms were not adequately described. Jaundice was present in twenty-nine cases. Cholecystography failed to visualize the gallbladder in fifteen cases. Stones in the region of the common duct were present in four cases. The gallbladder fossa in the liver was present in seven cases and absent in twenty-five. In twenty-eight no mention was made. The cystic duct was present in four cases and absent in forty-two cases. It was not mentioned in fourteen cases. The common bile duct was dilated in nineteen cases and normal in size in twenty cases. In twenty-one mention of the size was omitted. Carcinoma of the common bile duct with dilatation above the lesion was noted in one case. Gallstones were found in the common bile duct or the hepatic duct in sixteen of the cases. The liver was not enlarged in nine cases and cirrhosis was present in thirteen cases. Hepatitis was noted in five cases, the left lobe of the liver was absent in one patient. An unusually small quadrate lobe was seen in six cases. The pancreas was mentioned in only twelve cases; of these, eleven showed pancreatitis. Brief case history reports of the ten cases from the Mayo Clinic were presented.

Prolonged drainage of the common bile duct with a "T"-tube was advocated in cases in which symptoms were present. In one of their cases, the common bile duct was drained for two years despite the fact that no stones or dilatation of the duct was encountered at operation. In four other cases, in which symptoms existed, no drainage was employed and the patients continued to complain of the same symptoms.

**Anomalous Ducts** — Neuhof and Bloomfield<sup>9</sup> point out that a duct communication between the gallbladder and the liver is regularly found in fish, reptiles, and birds. Occasionally, this type of anomaly is encountered in man and they have called this anomalous duct the cholecystohepatic duct. The incidence of this duct is somewhat doubtful, although it is sufficiently frequent to give the surgeon some thought lest he overlook it and a subsequent biliary drainage or peritonitis develop. This condition may be treated by ligation or coagulation of the accessory ducts.

The authors cite the case of a fifty-eight-year-old female suffering from a four-day history of right upper quadrant pain and jaundice. The urine was dark, stools not observed. Dyspepsia had been present for a long time. The positive physical findings were obesity, slight icterus, marked tenderness, and increased muscle tone in the right upper quadrant with an orange-sized tender mass palpable. A preoperative diagnosis of common duct obstruction and distention of the gallbladder was made. A cholecystectomy was performed from the fundus downward. The cystic duct was about 3 mm. in diameter and after division several centimeters of dark viscid bile, containing a few crystalline particles but no stone, escaped from its stump. After this, clear yellow bile came from the common duct. No com-

mon duct calculi or dilatation was noted. The common duct was not opened, a No. 20 French catheter used to drain the common *via* the cystic duct. During the dissection of the gallbladder from its bed, an orifice about 2 mm. in diameter was discovered in the upper portion. Dark viscid bile escaped from this duct identical with the character of the bile which came from the gallbladder and cystic duct. After the dark bile had escaped, clear yellow bile followed. A fine probe could be passed from this orifice into the liver substance for a distance of 2 or 3 cm. Sections of the duct were removed for a microscopic examination. No other anomalies were found. The immediate postoperative course was uneventful. The catheter drain in the cystic duct was extruded within one week, rubber dams were removed within several days. On the eleventh postoperative day, the temperature rose to 102° F. and a small tube placed through the incision into a sinus drained bile freely. This biliary drainage continued until the forty-fifth day after operation. Follow-up studies showed that there was no recurrence of symptoms. Looking back at this case, the authors felt that ligation of the duct at the time of operation would have been preferable to leaving the duct open.

The second case was a female, aged sixty-three, who suffered from recurrent upper right quadrant pain for four years with gradual increase in the frequency and duration of the pain. Two weeks before admission, the patient had chills and fever for several days. There was never any jaundice noted. Physical examination showed tenderness and spasticity in the upper right quadrant with an enlarged palpable gallbladder. At operation, an enlarged gallbladder containing many stones, was separated from the liver bed. A biliary leak occurred

from the lumen of a duct which appeared to run from the gallbladder to the liver. This was confirmed by biopsy. It was closed by means of a suture. Postoperative course was uneventful. Follow-up showed a good result.

As a result of these cases, the authors emphasized the importance of recognizing these anomalous communications and suggest ligation of the duct in order to avoid prolonged leakage of bile, biliary peritonitis, or local infection in the postoperative period.

**Carcinoma**—The fact that carcinoma of the gallbladder is more common than is generally supposed is pointed out by Finney and Johnson.<sup>10</sup> The general incidence of the condition is about one-fourth to three-fourths of 1 per cent of all autopsies, or 5 per cent of all cancer disclosed at autopsy. Eight to 10 per cent of all cancer occurring in the female is primary in the gallbladder. In males, the incidence is from 1 to 4 per cent. This discrepancy has about the same sex ratio as the incidence of cholelithiasis. Cholelithiasis is present in from 75 to 80 per cent of all carcinomatous gallbladders found at autopsy. The authors feel that from 4 to 5 per cent of all calculous gallbladders may eventually be associated with malignancy of the organ. The authors pointed out in justifying their plea for cholecystectomy in the presence of gallstones, which were asymptomatic or silent, that a mortality rate varying from 1.5 to 2 per cent should be compared with a malignancy expectancy of 4 to 5 per cent.

Eighteen cases, two males and sixteen females, were reviewed. One occurred in the forties, three in the fifties, six in the sixties, seven in the seventies, and one in the eighties, with an average age of 67.4 years. Stones were present in all cases. In thirteen cases, there was a history suggestive of gallstones vary-

ing from one to twenty years preceding the operation. In four other cases, giving symptoms of less than one year's duration, the complaint seemed to be due to an already inoperable growth. In one case, the history was so indefinite that evaluation could not be estimated. Cholecystostomy had been performed in two of the cases, prior to the operation at which malignancy was found, one, twenty, and one, five, years before. Re-formation of stones had occurred in both these cases. Six cases survived the operation less than one month, three survived from one to three months, four from four to six months, two from seven to twelve months, two from thirteen to eighteen months, and one for twenty-five months. In three cases, the gallbladder was removed. In one of the cases, the presence of a growth in addition to stones was suspected but no evidence of extension demonstrable. Survival only 10.5 months. In the other two, early carcinoma was found on microscopic examination and both succumbed to the malignancy in 16.5 months and 25 months. These eighteen cases represented all the primary carcinoma of the gallbladder in a series of 1192 gallbladder operations or a percentage of 1.5.

As a result of this experience, a strong plea for early removal of all calculous gallbladders was made. It was pointed out that removal of the stones alone was not a sufficient prophylactic treatment. Histologically adenocarcinoma predominates, squamous cell carcinoma usually anaplastic is less common, and schirrous growths are frequent. The keloid type, with peritoneal extensions, is occasionally seen. Extension occurs by local infiltration of the gallbladder wall, then to the liver and adjacent tissues, by the lymphatics to the cystic node, and then to the nodes of the common duct. Distant metastases are rare and the liver is

usually involved at the time of operation. It was not felt that there was any syndrome which would be of value in making an early diagnosis of carcinoma of the gallbladder, and that the diagnosis was not important if one remembered the connection between cholelithiasis and malignant degeneration removing calculous gallbladders early.

Primary cancer of the gallbladder in eighteen cases is reviewed by Peco.<sup>11</sup> The frequency of this form of cancer was 0.15 per cent of all the cases admitted during the period of October 1, 1929, to July 31, 1944; 1.9 per cent of the cases of benign disease of the gallbladder; and 3.9 per cent of the 455 patients with gallstones. Seventy-two per cent were more than fifty years of age and 50 per cent were females. Cholelithiasis was seen in all cases in which the contents of the gallbladder were examined. Among the tumors, 87.5 per cent were carcinomas, the rest epitheliomas and mixed forms; 12.5 per cent of the carcinomas were of the villous type and 75 per cent of the infiltrative. In 60 per cent, the tumor site was known, in 26.6 per cent it was in the fundus, and in 26.6 per cent in the body of the gallbladder.

There had been a previous history of benign disease in 89 per cent, of which 67 per cent was typical hepatic colic; in 22 per cent, dyspeptic symptoms, and in 11 per cent, latent lithiasis. Pain was present in 67 per cent, obstructive icterus in 50 per cent, tumor of the gallbladder in 39 per cent, and weight loss in 89 per cent.

Without pathological examination, the clinical picture of beginning cancer of the gallbladder may simulate benign disease. To support the diagnosis in a patient with a history of cholelithiasis, the pain and dyspeptic symptoms recur and become more severe, continuous and

progressive. In less than six months after the beginning of the disease, death had occurred in 67 per cent. As the disease develops gradually, it isn't usually diagnosed until it reaches an advanced stage. Among the eighteen patients, six were operable, radical operations being performed on only two. The possibility of cancer developing in patients with gallstones should always be considered in determining the indications for treatment of gallstones.

### Roentgenology

Vaughan and Eichwald<sup>12</sup> claim an incident of 95 per cent accuracy for cholecystography. They point out that science is constantly striving to improve the chemicals and the technic for the procedure. The use of *priodax* (bilioselectan, as it was called in Germany) was first described by Kleiber in 1940; this dye was used on fifty-five patients and the results verified by surgical operation. In addition to the excellent contrast medium, it minimized the diarrhea, nausea, and vomiting. Priodax is a white odorless powder soluble in alkali, ether, alcohol, and acetone, but almost insoluble in water. Experimental study showed that the lethal dose with oral administration was 1000 mg. per kg. of body weight. Fifty per cent of the priodax used is excreted through the urinary tract, in contrast to the 10 per cent of tetraiodophenolphthalein when the latter is used. The remainder of tetraiodophenolphthalein is excreted through the gastrointestinal tract, which is undesirable from the roentgenologic viewpoint. Priodax is available in tablets of 0.5 gm. each, the dosage is 1 tablet per 25 pounds of body weight. Tablets should be swallowed with or without water, but should not be chewed.

It was observed by Boyden and Layne<sup>13</sup> that the gallbladder was not

visualized in 40 per cent of male patients with pernicious anemia as against 22 per cent as anticipated in normal male patients. In forty-eight patients suffering with pernicious anemia, the gallbladder was not visualized in 42 per cent, eight of twenty-three males (35 per cent) and twelve of twenty-five females (48 per cent). Out of 31,311 consecutive autopsies, the authors examined the protocols of 105 cases of pernicious anemia and found 32 per cent had had either cholecystitis or cholelithiasis, or that the gallbladder had been removed.

In male patients, the rate of emptying of the gallbladder was different from that of the female in that the curve of evacuation was not significantly different from that of the controls. In the female there was a highly significant retardation, the gallbladders discharging an average of 69 per cent of their contents in the first forty minutes after a standard meal as against 84 per cent in a control series. It is suggested that pernicious anemia sometimes causes a permanent narrowing of the choledochoduodenal junction.

### Gallstones in Relation to Cardiac Disease

Clark<sup>14</sup> points out that cholecystitis or cholelithiasis may stimulate or aggravate cardiovascular disease. The association of gallbladder disease and coronary sclerosis has frequently been demonstrated. It is also pointed out that a diseased gallbladder may act as a trigger mechanism initiating attacks of angina. If the angina patient is in relatively good condition, and has gallstones, cholecystectomy will not only relieve the gallbladder symptoms, but will often have a most favorable effect on the heart symptoms. He felt that it was a mistake to allow a patient to continue with what

had been called silent or innocent gallstones providing they were in relatively good condition in the forty or fifty age group. The subsequent risk of operation and complications as a result of these gallstones have frequently been pointed out.

### **Cholecystitis in Relation to Dermatosis**

Urbach and Shay<sup>15</sup> report the case of a woman, aged sixty-three, suffering from a severe light dermatosis which was cured by extirpation of an infected gallbladder. A pathological intestinal floor was found in this case as in others suffering from light hypersensitivity. This may have been the cause of the increased porphyrin content of the stool. The authors suggest two possible mechanisms through either of which the diseased gallbladder might have been responsible for the agent causing the hypersensitivity to light.

### **Statistical Studies**

A statistical study was undertaken by Bearse<sup>16</sup> to establish a more definite time relation between gallstones and their sequelae—acute cholecystitis, acute pancreatitis, common duct stones, and carcinoma of the gallbladder. Existence of stones in the gallbladder must be established before complication and sequelae of cholelithiasis can be anticipated. The time factor for the development of biliary complications must resolve itself into the time lapse between the onset of primary symptoms or demonstration of stones and the clinical onset of these complications.

Gallstone operations in 260 patients were studied. The average duration of symptoms was five and one-tenth years. At operation, 157 (60 per cent) presented no biliary disease other than gallstones. Symptoms were present for

thirty-nine years, average period being four and six-tenth years. One or more complications were found in 103 (40 per cent) at operation. These included acute cholecystitis, acute pancreatitis, cholelithiasis, and carcinoma of the gallbladder. Acute cholecystitis was found in 69 patients (27 per cent), including empyema, gangrene, and acute free perforation of the gallbladder. Duration of symptoms was four and nine-tenth years, similar to cases without complications.

A significant and fairly constant finding is the association of acute pancreatitis with gallstones, but there is no agreement concerning pathogenesis. In this series, 10 patients (4 per cent) had acute pancreatitis, 32 (12 per cent) had stones in the common duct. The average duration of symptoms was five and six-tenth years.

Timoney<sup>17</sup> reviewed a history of 151 patients with cholecystitis over a three-year period. There were 90 females and 61 males. Seventy-six per cent of the patients were between thirty and sixty years of age. Emphasis was placed on diagnosing accurately which was correct in all but 7 cases. This was attributed to the presence of x-ray evidence of stone, repeated nonfilling of the gallbladder during cholecystography, or the history, with symptoms and definite physical signs of an acute attack. The incidence of stones in the gallbladder was 75 per cent. A total operative mortality for all cases was 4 per cent with an operative mortality for chronic cholecystitis of 2.6 per cent. Cholecystectomy was performed in 96 per cent of the cases, 6 per cent requiring drainage of the common bile duct. The outstanding indications for common duct drainage were palpation of stones, a history of jaundice, multiple small stones in the gallbladder with a dilated cystic duct,



dilatation of the common duct, and enlargement of the head of the pancreas.

Excellent results are obtained when the diagnosis is correct. The author felt that the operation should be limited to those cases in which stones are present or where there is a history or presence of an acute attack.

The case histories of 100 patients who were operated upon during the last ten years were reported by Johnson *et al.*<sup>18</sup> Calculi were present in 17 patients. Accurate diagnosis was proven by cholecystography in over 90 per cent of the cases. Thirteen of the noncalculus cases reported permanent relief, 3 only temporary relief, and 4 were made worse by operation. The authors concluded that noncalculous cholecystitis is best treated medically, but upon failure of this treatment to bring relief, cholecystectomy was recommended. In the calculous type, surgery was considered necessary.

**Acute Cholecystitis** — Smith<sup>19</sup> reviewed 332 cases of acute cholecystitis. The ratio of females to males was two to one. Cholecystectomy was performed on 223 patients with a mortality rate of 3.5 per cent and cholecystostomy on 103 with a mortality rate of 11.6 per cent. Of 239 observed for a period of from one day to five weeks after admission before operation, 24 died (10 per cent). Ninety-two (30 per cent) were operated upon the day of admission with a mortality rate of 5.4 per cent. Cultures were taken in 228 cases; 20 per cent presented "no growth," *Bacillus coli* was found 70 times, *Streptococcus viridans* 23 times, *Bacillus welchii* 10 times, hemolytic streptococcus 5 times, *Staphylococcus aureus* 7 times, pneumococcus 2 times, hemolytic *Bacillus subtilis* 8 times, and typhoid bacillus 7 times. There were 24 deaths, a mortality rate of 7.2 per cent. One death occurred without operation. Twenty deaths occurred in patients

over fifty years of age. Gangrene or perforation or perforation with abscess was found in 20 per cent. Seven died of acute pulmonary complications, 5 cardiac and 2 renal. One died of sepsis, 2 of pulmonary emboli, and 1 survived this complication. One died of apoplexy and 2 of hyperpyrexia.

A cholecystostomy may be a lifesaving procedure. If the condition warrants, a secondary cholecystectomy should be done. Advanced disease elsewhere in the body may necessitate accepting a cholecystostomy. If the clinical course of the patient does not improve in twelve hours, surgery or more rigid medical supervision must be followed. Failure to improve in twenty-four hours demands surgical intervention. Improvement under medical treatment allows delay in surgical intervention.

Acute cholecystitis in 123 patients is reported by McGuigan.<sup>20</sup> There were 98 females and 25 males, ages varied from twenty-one to seventy, average being forty-six and one-half. All received essentially the same preoperative treatment: *Morphine* hypodermically, an *ice cap* to the *abdomen*, and parenteral infusions of *glucose solutions* to combat dehydration and fortify the liver. Post-operative management was also similar: *Morphine* for pain and *glucose solutions* to maintain the water balance and to supply sugar to the liver.

The material was divided into six groups according to length of time elapsing between the onset of the symptoms and the operation. Seventy-two hours was arbitrarily chosen as the dividing point between the immediate operation and the delayed procedure. The operative mortality in the first group, twenty-two patients, or those operated within a forty-eight-hour interval, was 13.6 per cent; in the second group, seventeen patients, between forty-eight and seventy-

two hours, was 11.8 per cent. The average of these two groups was 12.7 per cent. Group three, twenty cases, between sixty-two and ninety-six hours after onset of symptoms had a mortality rate of 5 per cent. Group four, twenty-four patients, from 96 to 120 hours, had a mortality of 4.2 per cent. Group five, twenty-three patients, 120 hours to 7 days, a mortality of 0. Group six, seventeen patients, from eight to ten days, mortality of zero. The average mortality in those operated after seventy-two hours was 2.38 per cent. The mortality for this series was 5.69 per cent, which compares favorably with other statistics.

The policy adopted as a result of this study was the expectant treatment of acute cholecystitis as long as delay results in improvement of the patient. Cholecystectomy was the operative procedure of choice and seemed to have a lower mortality than cholecystostomy. The policy must be flexible and in the presence of progression of signs and symptoms expectant treatment must be interrupted and operation performed. Cholecystostomy is only used in the aged individuals with conditions contraindicating cholecystectomy.

**Empyema and Gangrene**—Blumberg and Zisserman<sup>21</sup> reviewed a series of eighty-three cases of empyema and/or gangrene of the gallbladder. Thirty of these were male and fifty-three female. The age ranged from twenty-nine to seventy-two with an average of 53.3 years for men and 55.9 for women. A gallbladder history prior to the acute attack was given in fifty-four of these patients (66 per cent). In many cases, the history was that of gallbladder disease of moderate severity extending over a period of years sometimes as long as twenty years. An interval between the onset of the present attack of pain and its termination, by either operation or

death, was found to be twelve days for men and thirteen and one-half days for women. Some of the operative delay was deliberate since it was common practice at that hospital to operate on acute gallbladder patients only when necessary, by the presence of progressive lesion. The abdominal pain usually occurred in the right upper quadrant, the epigastrium, or as a generalized abdominal pain. Radiation was present in 50 per cent of the patients usually referred to the back right scapula or across the upper abdomen. Abdominal distention was rarely noted, marked tenderness was usually present and fairly well localized to the right upper quadrant. Chills and fever associated with the acute attack were noted in only nine cases. Nausea, vomiting or both were present in most of the cases. Jaundice was present in 10 per cent of the patients.

There was a history of preceding jaundice in only 6 per cent of the patients. An enlarged mass in the right upper quadrant was palpated in thirty-eight (46.3 per cent); could not be palpated in thirty-five (42.7 per cent). The remaining cases were doubtful. The temperature was of a sustained type rather than a septic one, with a peak as high as 103° F. in some cases, while in others it barely exceeded normal. The majority, however, had a moderate fever of approximately 101° F. The average blood pressure was 134/79 for men and 144/80 for women. The average white cell count was 15,660 for males and 15,870 for females, with neutrophil variation of 81.3 per cent and 80.2 per cent respectively. In many cases, the white count fell prior to surgical intervention. Since all of these patients had progressive and nonresolving lesions, the fallen blood count did not necessarily indicate pathological improvement.

TABLE I

	Group 1		Group 2		Group 3		Group 4		Group 5		Group 6	
Number of cases....	22		17		20		24		23		17	
Average age.....	49		52		42		45		41		50	
Average temperature....	101° F.		100.6° F.		99.8° F.		99.2° F.		99.2° F.		99° F.	
Average leukocyte count....	12,500		14,500		13,000		12,500		11,000		10,250	
	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent
<b>Operative Procedure:</b>												
Cholecystostomy.....	19	86.4	13	76.5	6	30	2	8.3	0	0	0	0
Cholecystectomy.....	3	13.6	4	23.5	14	70	21	87.5	22	95.7	17	100
Simple drainage.....	0	0	0	0	0	0	1	4.2	1	4.3	0	0
<b>Pathological Changes:</b>												
Acute catarrhal.....	13	59.1	8	47	10	50	1	4.2	0	0	0	0
Acute suppurative.....	6	27.3	3	17.7	4	20	4	16.7	1	4.3	3	17.6
Acute gangrenous.....	3	13.6	5	29.4	1	5	1	4.2	0	0	0	0
Empyema.....	0	0	1	5.9	5	25	15	62.5	13	56.5	1	5.9
Hydrops.....	0	0	0	0	0	0	2	8.2	4	17.4	8	47.1
Perforation with abscess formation.....	0	0	0	0	0	0	0	0	1	4.3	0	0
Perforation with generalized peritonitis.....	0	0	0	0	0	0	1	4.2	0	0	0	0
Subacute or chronic.....	0	0	0	0	0	0	0	0	4	17.4	5	29.4
<b>Postoperative Course:</b>												
Smooth.....	11	50	10	58.8	16	80	20	83.3	21	91.3	15	88.2
Stormy.....	11	50	7	41.2	4	20	4	16.7	2	8.7	2	11.8
Mortality.....	3	13.6	2	11.8	1	5	1	4.2	0	0	0	0

(McGuigan, W. J.: Am. J. Surg. 68: 225 (May) 1945.)

An analysis of twenty-one cases of advanced gallbladder disease, which had gone on to perforation, were reviewed. There were nine males and twelve females. In some cases these were well encapsulated by adhesions and only three were accompanied with widespread peritonitis. Rupture into the duodenum occurred in one instance. The average age was 61.8 for males and 57.1 for females. In this group, an antecedent gallbladder disease varied from a short interval to a very long one from fifteen to twenty years. In three cases the patient denied any previous gallbladder dysfunction. The average duration of the acute attack until its termination by operation or death was eleven days for

females and eight days for the males. A mass in the region of the gallbladder was palpated in one third of the cases. Pain was diversified, more widespread than with the other group and 50 per cent of the patients had pain across the entire upper abdomen. All patients with acute perforation experienced nausea and vomiting. The average blood count was 16,600 white cells and 82 per cent neutrophils.

Surgery was performed in seventy-three of the cases, 89 per cent of the entire series, with advanced gallbladder disease. The type of operation performed varied from a simple incision and drainage of the gallbladder to complete excision, the more serious cases receiving

the most simplified surgery. Cholecystectomy was done in approximately one half of the operative cases. In the perforated group, complete cholecystectomy was performed in only three instances, while fourteen were treated by simple incision and drainage. *Spinal anesthesia* was used in 81 per cent of the cases. Supplementary anesthesia was necessary in seven cases, the methods being *nitrous oxide-oxygen*, ether or intravenous *pentothal sodium*. Nine were operated under local anesthesia. In the perforated group, fourteen had spinal anesthesia and the remaining three local.

Stones were found in 79 per cent of the eighty-two cases and in two thirds of the patients with perforated gallbladder. In some cases, a search for stones was omitted due to the condition of the patient. There was a mortality of 25 per cent in the eighty-two cases with eleven deaths in the seventy-three submitted to operation or an operative mortality of 15.1 per cent.

The cause of death was :

1. Twelve, as a direct result of biliary tract disease.
2. Four, as a result of disease aggravated by the biliary disease.
3. Four, as a result apparently unrelated and not influenced by the biliary disease.

In the entire series there were thirteen diabetic patients, of which five were male and eight female with an average age of 61.4 years. Eleven of these were operated upon, two had cholecystostomy under local anesthesia, six cholecystostomies and three cholecystectomies under spinal anesthesia. The mortality for these cases was very high—seven (54 per cent). As a result of this, the authors considered diabetic patients to be poor risks for surgery in the presence of advanced gallbladder disease, and sug-

gested prophylactic cholecystectomy in the presence of gallstones accompanied with diabetes before the acute attack develops.

### Treatment

Bachhuber *et al.*<sup>22</sup> find in reviewing literature on surgical treatment of gallbladder disease that one is confronted with numerous clinical reports, advocating diametrically opposed types of therapy. In regards to the different types of pathological lesions, the clinical reports also show a great variation. They find the rate of advancement of the pathological process, the dangers of serious complications, and the dangers of certain types of therapy emphatically stressed.

They were prompted to undertake a study of gangrene and perforation of the gallbladder and allied conditions because of marked variation in the occurrence of gangrene and perforation of the gallbladder and resultant variation in the mortality rates. Between January 1, 1938, and January 1, 1942, a total of 1699 patients were admitted during an acute attack of biliary tract disease or for surgery following the subsidence of the disease. Of these, 115 (6.76 per cent) were found to be suffering from superficial or healed ulceration, 34 (2.0 per cent) from gangrene, 15 (0.88 per cent) from internal biliary fistula, 18 (1.05 per cent) from pericholecystic abscess formation, and 45 (2.64 per cent) from free perforation showing a total incidence of 1.36 per cent of some type of necrosis or gangrene.

Omitting the ulcerative group, gangrene and perforation occurred in 6.82 per cent. In patients suffering from internal biliary fistulae, gangrene, pericholecystic abscess, or free perforation on medical service, there were twenty deaths, nine deaths following operation

and eighteen nonoperative deaths on surgical service or 47 deaths, making an overall mortality of 2.76 per cent. Thirty-eight of these were nonoperative, which comprised 80.85 per cent of the total mortality, placing the surgical mortality at 0.53 per cent and medical mortality at 2.23 per cent.

The incidence of gangrene and perforation appears rather high but not as high as previously quoted statistics. To be fair, one would have to determine the number of acute attacks each patient experienced to determine correctly the possible danger of gangrene or perforation of the gallbladder. If the average attack per individual be placed at two, the danger of gangrene would be reduced 50 per cent. With no exact figures to present, the authors' opinion is that the average attack per patient before surgery if instituted is far above two, so the danger of gangrene developing from an acute attack is small. The deaths from the gangrenous group represent a mortality which must be considered.

The most important group in the reduction of mortality from biliary tract disease is the nonoperative or forgotten group. Little is heard of this group, yet if the adherents to the different types of therapy were to pause and give this group proper consideration, a substantial reduction in the mortality of disease of the biliary tract could be obtained. The lowering of this mortality could be undoubtedly accomplished if the public was educated to the fact that the removal of a diseased gallbladder is necessary as soon as possible, this would likewise stave off some of the serious complications at a later date. The more recurrent the attacks, and the older the age, the more possibility there is that the patient may also be suffering from some serious concomitant disease, all of which will contribute to the mortality.

The authors conclude that the danger of gangrene and perforation is overstressed by the group that favors immediate surgery. More attention should be given to the forgotten group through proper education, thereby bringing the patient to surgery at an earlier age. Neither delay nor early surgery will spare the patient who seeks hospitalization when he is moribund.

**Cholecystectomy in the Typhoid Carrier**—In reply to the statement made in the *Journal of American Medical Association* under Queries and Minor Notes, stating that removal of the gallbladder is not an accepted procedure to rid carriers of typhoid bacilli, Neader<sup>23</sup> referred to a report of eighteen typhoid carriers treated by cholecystectomy with sixteen apparent cures over a twelve-month period. He also points out that in other reports of the literature there is about 70 per cent recovery from the typhoid carrier state following cholecystectomy. The possibility of the organisms being lodged in the appendix or the urinary bladder was mentioned. He mentioned an eleven-year-old child who was deprived of schooling and social contacts as a result of chronic typhoid carrier state, who was able to resume normal life following cholecystectomy. The importance of complete removal of the cystic duct down to its junction with the common duct, thus avoiding the possibility of a pocket in the remaining cystic duct, was emphasized as a technical factor which may account for some failures.

Feemster and Smith<sup>24</sup> point out that various clinical biological agents which have been tried usually fail to cure chronic typhoid carriers. In these cases, a cholecystectomy should be considered. They review observations on sixty-eight typhoid carriers operated on in Massachusetts between 1924 and 1944. There

have been sixty-three cures and five failures. In order to establish that a patient is a bile carrier, it is necessary to demonstrate the typhoid bacilli in the bile by duodenal drainage prior to operation, or by culture taken from the gallbladder at the time of operation. A careful bacteriologic follow-up study for not less than twelve months, consisting of negative stool cultures and at least one negative bile culture, should be done. They feel that cholecystectomy is still the only effective method of curing typhoid carriers.

### Sequelae

In a study of their operations over a ten-year period and 1000 operations performed elsewhere, Mirizzi and Urrutia<sup>25</sup> studied the cases in which symptoms recurred following cholecystectomy. It was found that cholecystectomy gives complete cure in 95.8 per cent of the cases and that there are serious sequelae in 1.6 per cent and milder sequelae in 2.6 per cent. The serious sequelae are usually due to residual stones in the common duct overlooked at the first operation. The spastic disturbance of the sphincter of Oddi and pancreatitis account for the less serious sequelae. Infection is a secondary and not a primary cause of postoperative symptoms. It aggravates rather than produces the difficulty. Residual hepatitis is not an important factor. It usually improves after cholecystectomy. Adhesions may cause sequelae but usually there is an associated factor.

It is pointed out that the surgical treatment should be complete at the first operation since repeated operations are more dangerous and difficult. An immediate cholangiogram will make an accu-

rate diagnosis in 99.5 per cent of the cases and therefore reduce the unpleasant sequelae to a minimum.

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## LIVER

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### Liver Function Tests

According to Wilensky,<sup>1</sup> tests of liver function are not essentially diagnostic and can only confirm previously made diagnoses of liver disease. Repeated tests have more significance than a single test because they show progression or regression of the liver lesion. They are also of value in the prognosis and the optimum time of operation.

The quantitative condition and variation of the proteinemia and the abnormal variations of blood-clotting function are considered the most significant. Next were tests measuring the degree of jaundice. The dye tests were not considered of particular value, with the possible exception of phenoltetraiodophthalein, which gives the important information only in mechanical obstruction to the gallbladder.

### Hepatitis

**Amebic**—It is pointed out by Sode-man and Lewis<sup>2</sup> that amebic hepatitis indicates the earlier phase of amebic hepatic disease before frank abscess can be diagnosed. They present thirty-three patients, all adults and 88 per cent men, suffering from this condition. Pain in the region of the liver was a universal complaint. It varied from sharp and severe to dull and achy. It was constant or intermittent. Fever was present in all but one case, varying from 103° to 104°, was intermittent in thirteen, and accompanied by chills. The skin was sallow but jaundice was not usually present. Nausea, vomiting, weakness, and loss of weight were other symptoms which were not constant. A history of diarrhea may antedate the stricture for a period of years. The most important

physical findings were enlargement of the liver, tenderness in the liver, an average leukocytosis of 13,000 was noted in 88 per cent of the cases.

In order to make the diagnosis, one must first be aware of the occurrence of the disease. Jaundice in 15 per cent of the patients indicates the necessity for consideration of amebiasis as a cause of hepatitis with jaundice along with Weil's disease, infectious mononucleosis, and other specific types of hepatitis. Evidence of impaired liver function by various tests may be present. The early diagnosis rests upon finding intestinal ameba, roentgenologic demonstration of bulging or extension in the region of the liver with impairment of motion of the diaphragm, and the complement fixation test.

The early diagnosis, before pus can be demonstrated, may be effectively treated with emetin alone, thus avoiding the dangerous procedures associated with a high mortality rate. A diagnosis based on the criterion of characteristic pus will always be late and the chances of early preventatives and therapeutic treatment small.

**Epidemic**—Droller<sup>3</sup> reported that 63 diabetic patients out of approximately 450 patients attending a diabetic clinic suffered from hepatitis. Anorexia, loss of weight, and vomiting were the symptoms most frequently encountered. Due to the disturbance of carbohydrate metabolism, immediate complications occurred in a number of patients. Acute yellow atrophy of the liver caused death in two of the patients. Delayed complications were noted in eight patients, two died of cirrhosis, the remaining six were in ill health. The epidemic oc-

curred when there was a high incidence of the disease among the general population. It was thought that both syringe and contact transmission occurred.

**Serum Iron**—In normal individuals, the iron content of the serum is rarely more than 0.2 mg. The lower limit varies from 0.05 to 0.08 mg.

Brochner-Mortensen (1942) studied fifty patients with various lesions of the liver and bile passages and found that the serum iron increased to above normal in eighteen of the twenty-six patients with acute hepatitis (69 per cent); in one of five patients with cirrhosis of the liver, and in one of ten with jaundice caused by cancer or cholelithiasis.

In patients with hepatitis, determinations of serum iron showed great individual variations, the maximum being in the second week of illness. No constant relationship was shown between the variations in serum iron, icterus index, and the lipase values. The icterus index and, especially, the lipase value reached the maximum quite rapidly and then decreased at varying rates, while the variations in serum iron were often more protracted. Usually, the lipase value becomes normal first, at a time when the icterus index is still increased.

The cause of increase in serum iron in hepatitis is not definitely known. Increased absorption of iron from the digestive tract cannot cause it. It is likely due to the liberation of iron from the disintegration of liver cells rich in iron, while at the same time the liver fails to absorb the iron set free by the physiological decomposition of hemoglobin. It seems hard to explain why the bone marrow and spleen should not act temporarily as depositaries from the iron in place of the liver.

The finding of an abnormally high serum iron content is of value only as a supplementary means of diagnosis. It

has been found in other diseases—pernicious, aplastic, and hemolytic anemias.

### **Rôle of Hemorrhage in Hepatic Insufficiency**

Ireneus and Puestow<sup>4</sup> performed experiments to determine whether or not massive hemorrhage could produce enough damage to the liver to give rise to hepatic insufficiency. Twelve dogs were bled from the jugular vein. Predetermined amounts of blood were withdrawn every five minutes for thirty minutes so that the amount of blood removed was 30 cc. per kg. This amount of blood loss constitutes a sublethal hemorrhage. The hepatic function tests employed were the sulfabromphenolphthalein sodium test, the galactose tolerance test, the prothrombin time test, and the serum phosphatase test. The galactose tolerance test consistently showed results indicative of hepatic damage, the excretion of galactose being above normal in eight of the eleven animals. The prothrombin time was definitely prolonged in four of the eleven animals. The other tests gave results within the limits of normal. It is pointed out that if one or two tests give positive results, a certain amount of hepatic insufficiency exists, since these tests are so sensitive that a positive result must be considered significant. The wide margin of safety possessed by the liver, only from 30 to 40 per cent being necessary to maintain life, is possibly the explanation for the mild impairment of hepatic function found in these experiments. It was, therefore, concluded that a slight impairment of hepatic function resulted from acute massive hemorrhage.

### **Liver Pathology in Thyroid Crisis**

The importance of the liver in the pathology of thyroid crisis is emphasized by Ficarra and Naclerio.<sup>5</sup> This opinion



is based upon the following reasons:

1. The clinical picture of crisis closely simulates exhaustion resulting from hepatic hyperpyrexia.

2. Experimental evidence and the morbid anatomical findings indicate the close association between hyperthyroidism and the liver.

3. Boyce's results with the Quick hippuric acid test of liver function has been offered as proof of liver damage occurring as the result of thyroid disease.

4. The physiological imbalance and pathological changes in the liver due to anoxemia has been established. Anoxia in hyperthyroidism is common knowledge.

5. The interrelationship between hyperadrenalism, hepatic glycogenolysis, and the experimental production of toxic thyroid signs by injections of adrenalin has been emphasized.

Hyperadrenalism and hepatic anoxia, acting either alone or synergistically, may be the most important influences in the production of thyroid crisis. The hyperadrenalism may be the activator which depletes the liver of its glycogen. In this state of insufficiency, the hepatic anoxia resulting from hyperthyroidism produces a lethal effect upon the patient.

The pathological finding of anoxia in the liver of patients dying from thyroid crisis is well known. Such factors as tracheal obstruction, pulmonary edema, and other complications may interfere with aeration.

It was felt that the benefit derived by multiple stage operations may be partially explained by the fortification of the liver which occurs between the stages of operation. The preoperative preparation of thyroid patients with special attempt at fortification of the liver was thought to be the cause of preventing a crisis at Kings County Hospital, within the past two years. The pre-

operative regime followed was: (1) Complete *bed rest*; (2) *Iugolization*; (3) *sedation*; (4) *thiouracil* administered until BMR is normal (0.6 gm. daily); (5) *oxygen test* to combat anoxia and hyperthermia (three days); by placing the patient in an oxygen tent the psyche reaction can be better estimated; (6) *glucose* intravenously plus *amino acids* and *vitamin B<sub>1</sub>*; (7) *blood* transfusions; (8) *cardiac therapy*; (9) *psyche evaluation*.

### Tumors of the Liver

Warvi<sup>6</sup> suggests the following classification for primary tumors of the liver excluding tumorlike hyperplastic nodules in secondary tumors.

**True Tumors**—1. Hepatomas: (a) Liver cell adenomas; (b) liver cell carcinomas with or without cirrhosis.

2. Cholangiomas: (a) Adenomas of intrahepatic bile ducts, solid or cystic; (b) carcinomas.

3. Cholangiohepatomas of both liver cell and duct elements.

4. Tumors primary in the liver but not of specific hepatic element (vascular, fibrous, adrenal rests, etc.). In a series of 353,971 admissions, 73 cases were diagnosed clinically as primary carcinomas of the liver. Due to error in diagnosis, there were probably 53 cases or an incidence of 0.015 per cent. This incidence is much higher in tropical countries and the clinical diagnosis is higher. It is seen from the table (Table I) the incidence of various signs and symptoms in primary carcinoma of the liver. The differential diagnosis of benign malignant and secondary malignant tumors of the liver is well tabulated.

Treatment of liver tumors must be surgical. X-ray therapy is ineffective and harmful. All localized liver tumors without evidence of involvement of adjacent organs, or too much of the liver

TABLE I  
FREQUENCY OF SYMPTOMS AND SIGNS IN PRIMARY CARCINOMA OF THE LIVER

<i>Symptoms and Signs</i>	<i>37 Proved Cases Reported in of C.G.H. (Per cent)</i>	<i>500 Proved Cases Reported Literature (Per cent)</i>	<i>134 Cases Reported by Tull (Per cent)</i>
Anemia . . . . .	97	68	38
Weakness and weight loss. . . . .	94	88	88
Palpable tumor . . . . .	91	68	68
Jaundice. . . . .	80	34	34
Pain. . . . .	71	52	10
Fever. . . . .	52	34	38
Vomiting. . . . .	44	12	2
Edema of legs . . . . .	40	60	84
Ascites. . . . .	37	46	48
Fixed diaphragm. . . . .	18	30	38
Tender liver. . . . .	15	17	15

itself, should be resected surgically. The best method is probably a combination of hemostatic sutures and electrocautery. A review of the literature indicates that 223 resected cases have been fully reported but probably a total of about 570 cases with limited description is included. The operative mortality was not high and most failures were due to inadequate removal with recurrence. The postoperative complications were largely those of metabolic disturbances such as early "liver death," late "hepatorenal syndrome," or finally malnutrition with loss of resistance to infection.

A detailed history of three patients with liver tumors was presented. One, a forty-five-year-old male with a right subcostal mass of one year's duration, associated with dull pain, from whom a typical adenoma of the liver cells was successfully removed. This patient died three years and five months after the operation of portal and biliary obstruction. The second case, a forty-two-year-old female, has remained in good health for eight and one-half years after surgical excision of an adenoma of the islet cell which was surgically excised. The third case was a thirty-eight-year-

old Negro who had pain in the middle of the back of seventeen months' duration, a tender epigastric mass the size of a golf ball, and a loss of twenty pounds in six months. Laparotomy at another hospital showed what was thought to be an inoperable carcinoma of the liver. This was removed by a Bovie knife, suturing the liver with No. 2 chromic catgut as the resection progressed. The patient improved following operation and was well twenty-nine months later.

The incidence of primary carcinoma of the liver in the African Negro and the American Negro is compared by Kennaway.<sup>7</sup> As a result of the much higher incidence of primary cancer of the liver in the African Negro, he concluded that it was not a primary racial characteristic. It was thought that the prevalence of this form of cancer in Africa may be due to some unidentified extrinsic factor. The statistical evidence concerning this question is confused by the inclusion of cancer of the gallbladder in the same category with cancer of the liver.

That primary carcinoma of the liver is a problem of major importance in South African medicine is pointed out

is based upon the following reasons:

1. The clinical picture of crisis closely simulates exhaustion resulting from hepatic hyperpyrexia.

2. Experimental evidence and the morbid anatomical findings indicate the close association between hyperthyroidism and the liver.

3. Boyce's results with the Quick hippuric acid test of liver function has been offered as proof of liver damage occurring as the result of thyroid disease.

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Treatment of liver tumors must be surgical. X-ray therapy is ineffective and harmful. All localized liver tumors without evidence of involvement of adjacent organs, or too much of the liver

rate of neoplastic growth, complications, and metastasis. The author divided his cases into five clinical groups as follows:

1. Frank cancer, *i. e.*, with symptoms of primary liver involvement (63.6 per cent of the cases).

2. Acute abdominal cancer, *i. e.*, with symptoms associated with an acute abdominal catastrophe (9.1 per cent).

3. Febrile cancer, *i. e.*, with fever as a salient clinical feature (7.6 per cent).

4. Occult cancer, *i. e.*, in which malignancy is discovered accidentally (15.1 per cent).

5. Metastatic cancer, *i. e.*, with symptoms referable to the organs involved by metastasis rather than to the liver (4.6 per cent).

The diagnosis is based upon clinical findings with microscopic examination of the pathological material obtained at operation or biopsy. Roentgenologic ex-

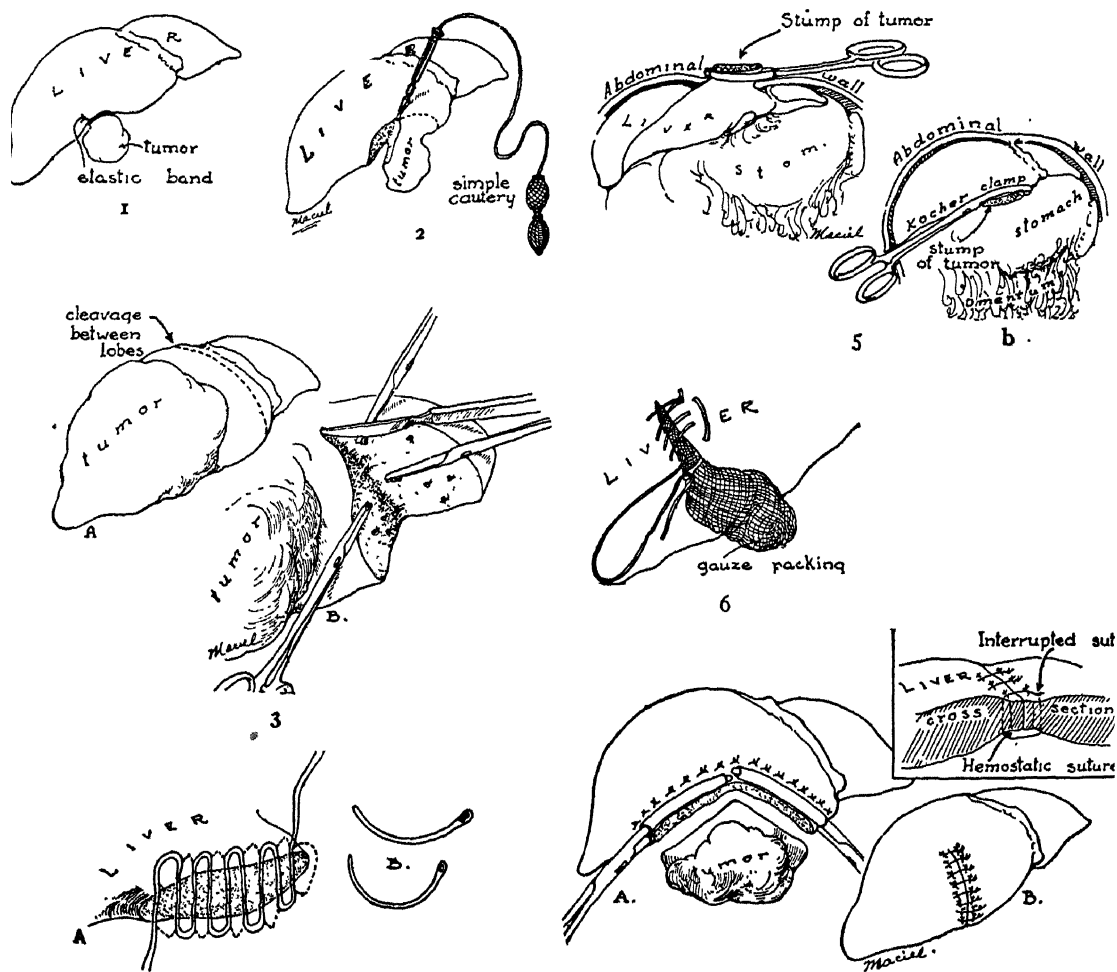


Fig. 1—Major methods of resection: 1, Elastic ligature and extraperitonealization of the stump (Cousins, 1874). 2, Simple cautery (Paquelin) removal (Escher, 1886). 3, Lobectomy with reported less bleeding for physiologic line of cleavage used (Langenbuch, 1888). 4, Hemostatic suture with blunt needle and closure of liver surfaces after resection (Kousnetzoff and Pensky). 5, Clamps left on for hemostasis, and, *a*, completely exteriorized (Lapoint, 1897) or *b*, only the handles exteriorized for removal through a stab wound (Kocher, 1902). 6, Excision with tamponade (Anschutz, 1903). 7, Hemostatic sutures placed proximal to clamps and electrocautery excision of tumor distal to clamps. Raw surface closed by interrupted sutures going around the longitudinal hemostatic sutures, preventing cutting of sutures through liver tissue. (Warvi, W. N.: Surg., Gynec. & Obst. 80: 649 (June) 1945.)

amination is of value in suspected metastatic cancer. Verification of the diagnosis, however, is often established only at autopsy. All liver function tests are of doubtful value. The Takata Ara tests may be of value in the diagnosis. This is a flocculation test of serum with a mixture of sodium carbonate and mercuric chloride.

The following diseases must be considered in the differential diagnosis:

*In Frank Primary Liver Cancer*—Neoplasms of the pylorus, transverse colon, pancreas, or right kidney, including their metastases to the liver; cirrhosis, syphilis, chronic venous congestion, or cystic disease of the liver, cholelithiasis, abdominal tuberculosis, leukemia, Banti's disease, and amyloid disease.

*In Acute Abdominal Cancer*—Volulus of the small intestine, perforated gastric, duodenal, or ambulatory typhoid ulcer, ruptured liver or spleen, biliary or renal colic, acute appendicitis, pancreatitis, and mesenteric thrombosis.

*In Febrile Cancer*—Amebic liver abscess, intrahepatic suppuration hydatid cyst of the liver, malaria, and subphrenic abscess.

The outlook is hopeless as the disease is rapidly fatal. Indications of approaching death are sudden enlargement of the liver, rapidly intensifying jaundice, increased dilatation of the superficial abdominal veins, and additional edema of the extremities.

The treatment is essentially palliative and directed toward the relief of pain and discomfort. Sedation in large and increasing doses is required. Attempts at radical surgical cure have usually been unsuccessful due to metastases in other parts of the liver. The value of x-ray and radium therapy could not be adequately studied due to lack of facilities.

Spontaneous cholecystoduodenal fistula associated with primary hepatoma of the

liver is exceedingly rare. Pomeranz *et al.*<sup>9</sup> point out that the diagnosis can be made preoperatively by means of roentgen studies. They report in detail such a case in which the diagnosis was made by roentgenogram and fluoroscopic studies. Barium extended in a linear streak near the superior portion of the duodenum, and surrounded a negative shadow. At the end of four hours there was 7 per cent retention of barium in the fundus of the stomach on the lesser curvature evidently resting against the left lobe of the liver. Speck retention of barium was also seen outside of the duodenum in the region of the previously described negative shadow. The gallbladder was not visualized. Reexamination of the gastrointestinal tract revealed that barium had extended into the gallbladder and a diagnosis of cholecystoduodenal fistula, with stone in the cystic duct, was made. Liver enlargement was noted clinically and also on x-ray examination.

The authors state that ninety cases of spontaneous biliary fistula have been reported in the literature. The most common cause of the fistula is chronic gallbladder disease with the formation of calculi which eventually perforates into the intestinal tract. The incidence of primary carcinoma of the liver is low, its average being 0.2 per cent. The diagnosis of primary tumor of the liver with cholecystoduodenal fistula diagnosed postoperatively and confirmed at surgery and autopsy is extremely rare. Although rare, the diagnostician should keep this possibility in mind.

Aspray<sup>10</sup> reports a case of calcified hemangiomas of the liver. Extensive circumscribed calcified shadows were demonstrated in the region of the gallbladder on roentgen examination of the abdomen. Within this circumscribed area, streaks of calcification seemed to radiate out

from the center. Impression was that of a benign neoplastic involvement of the liver, possibly hemangiomas. This was confirmed at autopsy.

### Embolus of the Liver

Martin and Wenzel<sup>11</sup> state that after a fairly extensive search of standard texts on proctology, no case of liver embolus as a complication of hemorrhoidectomy can be found. They report a case of a forty-three-year-old male who was admitted to the hospital for hemorrhoidectomy. He complained of constipation and slight bleeding. Had been treated eighteen months for tabes dorsalis and reported no symptoms other than numbness around the waist. System history was normal. Internal hemorrhoids and a small polyp were present. Rectum and pelvic colon were normal. Kahn reaction was 4 plus, urinalysis and blood count normal.

Under caudal anesthesia, a small anal polyp and internal hemorrhoids were excised, using composite technic of placing plain catgut ligature above each hemorrhoidal area followed by excision—no sutures for approximation. One plastic isthmus was created by connecting the rectal mucosa to the skin. Postoperative course was uneventful and patient was discharged on the fourth postoperative day.

During his ride home, he was conscious of considerable jarring. At 9.30 P. M. he was seized with constant, severe, generalized, upper abdominal pain, followed by a chill and recurrent nausea. No rectal pain. He returned to the hospital on the fifth postoperative day by ambulance. On admission, his temperature was 101.5° F., pulse 90, respiration 27, point tenderness in the right upper quadrant in the nipple line, 3 cm. below the costal margin. Abdomen was too

tender for deep palpation; leukocyte count, 12,250.

On the sixth postoperative day, temperature was 103° F., corresponding pulse elevation but normal respiratory rate. The liver was enlarged and tender. No ascites. Leukocyte count was 25,800. Blood culture taken proved negative. Icteric index was normal. Few red blood cells in urine. A diagnosis of "infectious hepatitis, probably embolic" was made. *Sulfathiazole* therapy was started—4 gm. at once and 1 gm. every four hours. After five days, temperature, pulse rate, and respiration were normal. Leukocyte count was 10,650; blood sugar, 105 mg.; icteric index, 2; direct Van den Bergh, negative; sulfathiazole blood level, 2.3 mg. A chill occurred on the eleventh day. Temperature rose to 102° F. on the twelfth day, icteric index was 7, and sulfathiazole was discontinued. On the thirteenth day, temperature rose to 105.4° F., icteric index was 3, white count was down to 9300, blood culture negative. Liver enlargement had disappeared and pain was gone. Forty-eight hours later, temperature, pulse rate, and respiration were normal, and remaining convalescence was uneventful. Liver function was proven to be normal by glucose tolerance curve.

Patient recovered and was discharged on the twenty-fourth postoperative day. In conclusion, the authors stated that there probably would have been a fatal outcome had it not been for sulfonamide therapy.

### Hepatic Vein Obstruction

Occlusion of the hepatic veins was found by Kelsey and Comfort<sup>12</sup> to be an incidental finding in sixteen of twenty cases. In the remaining four, it played a major rôle in the illness. Occlusion in all cases was due to thrombosis. It may be primary or secondary to inflamma-

tory, cirrhotic, or neoplastic diseases of the liver, thrombosis of the neighboring vena cava, diseases in which thrombosis occurs frequently and perhaps to slowing of the circulation in debilitating diseases. It is often merely an incidental observation at autopsy, yet it should be suspected when an acute painful episode with shock occurs during a chronic course of hepatic disease.

The rapidity of increase in the size of the liver and evidence of profound disturbances of hepatic function and portal obstruction may suggest the correct diagnosis. Acute occlusion has been confused with acute pancreatitis, but pancreatic lesion is ruled out by normal serum amylase findings and a rapidly enlarging liver and rapid development of portal obstruction.

Five cases of hepatic vein thrombosis were reported by Armstrong and Carnes.<sup>13</sup> The disease is rare and approximately sixty cases have been reported. The thrombosis occurs most frequently where the hepatic vein empties into the inferior vena cava probably because of eddy currents formed at the oblique entering angle. As thrombosis of the hepatic vein is often accompanied by inflammatory changes in the inferior vena cava it is probable that the two processes are continuous. The thrombosis may be partial or complete or complete with recanalization. Postmortem examinations revealed a characteristic central necrosis of the liver lobules, congestion of blood in this locality, replacement fibrosis of the liver, and splenic enlargement.

Obstruction of the hepatic veins has been equally distributed between males and females. The youngest person was seventeen months and the oldest seventy years of age. It occurs most frequently between the ages of twenty and forty years. It may occur in the acute or

chronic form. Pain over the liver—sometimes radiating to the back and shoulders rapidly accumulated ascites, resistance to diuretics, simultaneous enlargement of a smooth-edged liver and spleen, development of collateral circulation, and edema of the legs suggest obstruction of the hepatic veins. This condition is rarely diagnosed during life, as the clinical picture is that of obstruction of the portal veins and hepatic insufficiency. These five cases were observed in 11,979 autopsies, an incidence of 0.042 per cent. In three cases, the thrombosis was unimportant as a cause of death and probably occurred just before the patient died. In two cases, there was recanalization and some collateral circulation.

### Experimental Production of Portal Thrombosis

In a series of dogs, Brunschwig *et al.*<sup>14</sup> demonstrated that a collateral circulation could be established by gradually occluding the portal vein by means of a transfixion ligature. This was done by passing a linen thread about the portal vein proximal to the entrance of the gastrosplenic vein. The long ends were brought out of a wound and tied over the back. On the fourth day the threads were pulled up for a brief period and this procedure was repeated each day subsequently. On the twelfth postoperative day, the intact loop was pulled out, indicating that it had passed through the portal vein. Occlusion of the vein with division did not always occur, and in some cases a lumen persisted or reformed, but stenosis was noted at the transfixion site. These experiments indicated that a period of ten days was adequate for the development of venous collateral circulation following which survival may occur. The high incidence of peritonitis was attributed to the persistence of sinuses due to ligatures,

which became contaminated and automatically pulled up and relaxed. After this ligature transection of the portal vein, a second laparotomy could be performed with excision of a segment of the portal vein which the animals survived.

### Protein Metabolism of the Liver

The relationship of protein nutrition to diseases of the liver was discussed by Stare and Thorn.<sup>15</sup> Impairment of liver function in cases of cirrhosis due to replacement of liver tissue by fibers and fatty tissue, and the attendant portal obstruction with interference of normal gastrointestinal function, results in severe malnutrition. Since most of the components of the blood plasma are synthesized in the liver, a protein deficiency very often occurs. The specific manner in which liver damage involves protein metabolism is not precisely known; however, the difficulty with which the serum albumin level is maintained in patients with advanced cirrhosis is common knowledge. The advantages of a *diet* high in *protein* and *vitamin B* complex as well as *carbohydrate* has been adequately demonstrated in patients suffering from cirrhosis of the liver with ascites. The administration of such a diet may be attended with difficulty. Tube feeding is contraindicated due to the possibility of hemorrhage from esophageal varices. The administration of human *plasma* and *albumin* intravenously is beneficial. Recent studies indicate that "salt poor" concentrated human albumin solutions intravenously are particularly effective in increasing serum albumin levels and in promoting a diuresis in patients with generalized edema and ascites.

The value of protein in the treatment of hepatitis is also discussed. The use of *sulfur-containing amino acids*, *methionine*, and *cystine* were thought

to be of particular importance in protecting the liver from toxic hepatitis. Specific suggestions in the management of patients with cirrhosis and hepatitis follow:

1. A daily intake of 75 to 150 gm. of protein, 300 gm. or more of carbohydrate, and 50 gm. of fat is recommended. In general, it is possible to consume 100 gm. of protein with three daily meals. The remainder of the protein may be provided in supplementary high-protein feedings.

2. In the absence of esophageal varices, tube feeding with high-protein mixtures may be undertaken.

3. Approximately 10 mg. of thiamine, 10 mg. of riboflavin, 250 mg. of niacinamide, and 500 mg. of ascorbic acid are given daily during the first three or four days. Later the dosage of all these vitamins may be reduced to approximately one fifth of these quantities. Choline chloride or methionine may be given in enteric capsules 1 gm. twice a day.

4. Intravenous administration of protein, carbohydrate, and water-soluble vitamins may be indicated, depending on the condition of the patient. Recent studies suggest that a concentrated solution of "salt-poor" human albumin, administered intravenously, may result in a striking rise in serum-albumin level and in the replenishment of depleted protein stores.

The rôle of protein in surgery was discussed by Lund and Levenson.<sup>16</sup> Losses of protein may be from the intestines, through the kidneys, from any wound or orifice of the body, in internal exudates and transudates, and from any pathological condition of the skin that causes oozing or disquamation. Inadequate protein intake and diseases of the liver frequently cause protein deficiency. Generally speaking, losses from the intestines are important only in the presence of copious or long continued bleeding, diarrhea, or vomiting, or due to feeding diets which contain large amounts of roughage. The loss of protein which accompanies any surgical procedure or acute trauma from any cause was discussed.



It was pointed out that hypoproteinemia edema occurred in surgical patients only when the protein depletion is extreme. However, depletion of a lesser degree interferes with wound healing, gastrointestinal function and often leads to the formation of decubitus ulcers. This may lead to obstruction of a gastrointestinal anastomosis which further interferes with the protein intake. The importance of protein metabolism in gastric and duodenal ulcers, chronic ulcers of the skin, surgical traumatic, hemorrhagic and burn shock, and the resistance to infection was discussed.

The rôle of the liver in protein depletion with its subsequent decrease in size, softening and replacement by fatty tissues is well known. It was pointed out that biliary obstruction, chloroform anesthesia, and arsphenamine therapy will markedly increase the damage to liver cells if a hypoproteinemia is associated. The fact that an injured liver cannot manufacture albumin or prothrombin as well as a normal liver was pointed out.

The factors necessary for the evaluation of the status of a surgical patient suffering from protein deficiency are: (1) Weight of the patient; (2) observed weight of the patient; (3) plasma protein level; (4) plasma albumin level; (5) plasma volume; (6) nitrogen intake; (7) nitrogen output. Clinically, the main points are the patient's weight, the nutritional history, and the serum protein content determinations.

It is pointed out that acute conditions may mask or intensify chronic ones, depending upon the change which occurs. A patient with depleted body protein and a normally low plasma protein level may by reason of vomiting become dehydrated when the plasma protein concentration will become normal. Restoration of blood volume by electrolytic solutions will allow the plasma proteins to fall

below normal level. In general, acute depletions from any cause produce a loss of albumin faster and to a greater extent that the loss of the globulin, and the albumin is more slowly restored to normal. A normal plasma protein value will mask a severe hypoproteinemia when the globulin level is high.

The difficulty in obtaining and tolerating a high protein diet by mouth is discussed. Feeding by intubation in amounts of 200 cc. at one time, starting with half skim milk and half water, or with a mixture of protein hydrolysate and carbohydrate is pointed out. The possibility of continuous drip feeding is also discussed. The importance of additional vitamins in doses of 500 to 1000 mg. of vitamin C; the amines, 20 to 40 mg.; riboflavin, 20 to 40 mg., and niacin, 150 to 300 mg., should be considered in these cases.

The treatment of surgical shock or acute hypoproteinemia—by intravenous route with human *blood*, *plasma*, and *albumin* or a combination of these three—is often necessary to restore circulation. The authors feel that the best indication of restoration of circulation is a normal output of urine with a specific gravity of 1.010 to 1.025.

### Studies of Dextrose Content in the Liver

As a result of observations made on biopsy specimens of the liver taken from a group of fifty-eight patients with disease of the biliary tract, Zintel *et al.*<sup>17</sup> report that the average glycogen level of the liver of patients who received dextrose intravenously was 6.1 per cent or 118 per cent greater than the average glycogen level of a control group. This group consisted of eighteen patients who received dextrose and forty patients who were used as controls. The patients who

had moderate hepatic damage as judged by the histological studies and who received intravenously dextrose had an average hepatic glycogen level of 5.7 per cent or 104 per cent more than the level observed in the control patients. Intravenous dextrose without dietary supplement did not significantly lower the fat content of the liver in the patients observed.

It is stated that the protection of the liver against damage resolves itself into the positive action of protein, the indirect action of carbohydrate, and the negative action of fat. A diet high in carbohydrate and protein and low in fats and high in calories for five days or more before operation is excellent from the standpoint of reducing the liver fat, but does not appreciably elevate the glycogen level. The average increase in liver glycogen after such a diet in patients with severe hepatic damage was 10 per cent. On the other hand, there was no evidence that intravenous dextrose significantly lowered the fat content.

As a result of these findings, the optimum preparation of patients with hepatic damage for surgical operation would probably be obtained with the administration of a diet high in protein and carbohydrate and low in fat for a period of five to fourteen days, supplemented by intravenous administration of dextrose for a period immediately prior to operation. Liver glycogen is so labile that if one desires to maintain it at a high level, during an operation, intravenous administration of dextrose is fully justified. It was pointed out that as much as 45 per cent of the liver glycogen may be lost during the course of a long operation.

### Portal Hypertension

In order to understand the pathogenesis, the pathology, the diagnosis, and treatment of portal hypertension, Whip-

ple<sup>18</sup> reviewed certain points in the anatomy and physiology of the circulation of the liver and the spleen. It was pointed out that in the normal liver, the portal vein carried a large volume circulation at a low pressure, and that the hepatic artery carries a small volume circulation at a high pressure. There is a common channel of exit, the hepatic vein for fluid entering by these two circulations. The liver framework is freely expansible and these two circulations may affect each other by direct communication or by lateral pressure. Both sets of vessels are controlled by a vasomotor system. In the normal liver, a rise in portal pressure of 1 mm. occurs for each 40 mm. rise in arterial pressure; whereas in the cirrhotic liver there is a rise of 1 mm. in the portal circulation for each 6 mm. rise in arterial pressure. In cirrhotic livers, a large portion of the fluid escapes from the portal vein by means of collaterals, and only 13 per cent could be recovered from the hepatic vein as compared to 100 per cent in the normal liver. As the portal cirrhosis increases, portal blood passes through established collaterals, but as this pressure increases, rupture of these vessels may occur. In these cases, the hepatic artery is conveying most of the portal blood to the parenchyma of the liver. When the fibrosis increases to the point of shutting off arterial supply, parenchymal insufficiency develops.

It is pointed out that modern opinion, concerning the vascular bed of the spleen, combines the theory of an open component in the vascular bed. This permits the flooding of the splenic pulp spaces with whole blood with additional pathways available, by means of which the extravascular detour of the pulp spaces may be short-circuited, by direct communications between the arterioles and the venous sinuses. It is uncertain whether

arterial venous connections are structurally intact vascular tubes, or whether their appearance may be accounted for on a purely functional basis, such as an alteration in the porosity of the pulp caused by contraction of the splenic musculature. In order to settle the pathogenesis of many splenopathies, it is essential to settle the controversy over open or closed circulation in the spleen; and whether the arterial capillary terminates freely in the reticular meshes of the splenic spaces or directly into the venous sinuses. The author was definitely of the opinion that the splenic pulp spaces provide the one and only link between the arterial and venous systems in the mammalian spleen.

The amount of portal bed obstruction, the type, and the site of obstruction are variable factors in individual patients suffering with portal hypertension. An analysis of these factors in individual patients will determine the diagnosis, treatment, and prognosis in each instance. The intrahepatic portal block occurs chiefly in cases of cirrhosis of the portal or Laennec type. In another group, the so-called extrahepatic portal block, two types of obstruction are encountered. The first is a replacement of the vein or its main tributaries with fibrous tissue or scar tissue and little or no canalization. The second is a transformation of the portal vein or its tributaries into a cavernomatous mass of small tortuous vessels. Inflammation, trauma, or pressure from without by inflammatory or neoplastic tissue usually causes the thrombosis. An extension of the obliterative fibrotic process that takes place in the umbilical vein and ductus venosus, extending into the portal vein, may account for the early cases with a Banti's syndrome. These cases fortunately are rare. The pathogenesis of the cavernomatous transformation is un-

known. It may be an angioma, or cavernoma, or some other congenital anomaly.

When the portal vein is blocked and the liver is unobstructed, collateral circulation occurs through the accessory veins of Sappey, passing through the peritoneal covering of the liver, or from the stomach, and passing into the stem of the portal vein or the substance of the liver, the epiploic veins of the gastrohepatic omentum, the hepatocolic and the hepatorenal veins, the diaphragmatic veins, and the veins of the suspensory ligament of the liver. With an intrahepatic block, the shunt is by the esophageal veins to the azygos and the inferior vena cava *via* the middle hemorrhoidal veins, *via* the veins in the round ligament of the liver, and *via* the veins of Retzius. These are found within the abdomen where the gastrointestinal tract and its appendages for the organs developing from it become retroperitoneal developmentally.

It is pointed out that intrahepatic block may be produced experimentally by repeated injections of finely divided particles of silica into the splenic or portal veins. An extrahepatic block is more difficult to produce, but could be done in about one half of the animals where a cellophane band had been placed around the portal or splenic veins.

The syndrome of portal bed block with splenomegaly is fairly typical, whether the block is intra- or extrahepatic. It consists of a variable secondary anemia, a leukokemia, a thrombocytopenia, a splenomegaly, and a tendency to repeated severe gastrointestinal hemorrhaged, mostly associated with ruptured esophageal varices. This may or may not be associated with cirrhotic changes in the liver. The syndrome is spoken of as Banti's. The cause of Banti's syndrome is somewhat variable, and a case is mentioned where a ruptured

pancreas produced a Banti's syndrome which was cured by splenectomy. The splenic vein had been obstructed by dense scar tissue at the site of injury to the pancreas. The author was of the opinion that Banti's syndrome was a result of mechanical obstruction to the flow of blood within the portal bed. This may occur within the liver as in cirrhosis or in the extraportal type of block. Whether the portal block was intra- or extrahepatic may be determined by certain liver function tests. If there is a high retention of the bromsulphalein in the blood, if the hippuric acid test is positive, if there is a reversal of the albumin globulin ratio, or if the cephalin flocculation test is positive, the presence of a cirrhosis with intrahepatic portal block is fairly certain. On the other hand, if these tests are negative, it is safe to assume that the block is extrahepatic. Patients with normal liver function and a history of antecedent pancreatitis or trauma to the epigastric region point to the diagnosis of splenic vein thrombosis. Young children with normal liver function tests, giving a history of hematemesis, should lead to the diagnosis of portal vein occlusion as a result of continuation of the obliterated process in the umbilical vein and ductus venosus.

The factors indicating surgical treatment are the site of the block, the degree of the portal hypertension, and the extent and competency of collateral circulation. The size of the spleen and the incidence of gastrointestinal bleeding definitely call for surgical therapy. This may consist of splenectomy, since the spleen carries approximately 40 per cent of the total portal circulation. If the portal block is in the splenic vein, removal of the spleen results in a permanent cure with disappearance of the Banti's syndrome. The authors had only five such cases. Attempts at establish-

ing collateral circulation by omentopexy is questionable, especially in the presence of well established dilated collateral venous circulation on the abdominal wall. This may be demonstrated by infrared photographs. Attempts to ligate veins of the cardia and esophageal varices have been disappointing. Efforts to anastomose the mesenteric vein to the spermatic, ovarian, and the inferior vena cava have failed. Using a nonsuture method of blood vessel anastomosis, as described by Blakemore, the splenic and left renal veins were anastomosed in five cases after removal of the spleen and left kidney. In the last five patients, the portal vein was anastomosed to the inferior vena cava end-to-side. All of these patients survived operation. The procedure is still experimental and reserved for patients who have had repeated severe hemorrhage, which failed to respond to conservative measures. In five patients there was marked improvement in the liver function tests, disappearance of ascites or hemorrhage, encouraging the author to continue this work.

Blakemore and Lord<sup>19</sup> point out that a splenorenal anastomosis is capable of handling a large volume of blood and has the advantage of eliminating a sizable portion (estimated at 40 per cent of the total portal volume). The disadvantage of this is sacrifice of the left kidney. The technic is as follows:

Spleen is mobilized, vasa brevia are ligated with transfixion sutures and the gastrosplenic omentum cut through. The tail of the pancreas is separated from the splenic pedicle and the phrenocolic ligament is cut. A full length of the splenic vein is prepared, hemorrhage from the spleen may be controlled by strengthening the transfixion sutures around the splenic artery. The splenic vein is then clamped by means of a rubber-shod clamp. Immediately after the removal of the spleen, the splenic vein should be opened and thoroughly irrigated with saline solution. In order to make a satisfactory

anastomosis, the splenic vein should be mobilized for a distance of 8 cm. or more. Careful ligation of the small pancreatic branches may be necessary to accomplish this. Silk is used throughout for all ligations. The left kidney is approached through a transperitoneal route, retracting the descending colon medially. The kidney is mobilized, accessory vessels ligated and divided, division and ligation of the ureter, careful separation of the renal artery and vein with ligation of the artery. The renal vein

covered end of the splenic is inserted into the renal stump, being certain that neither is twisted. The rubber-shod clamp is released from the splenic vein immediately following the release of the clamp from the renal vein. Any tendency towards angulation should be corrected. The use of a vein graft for this anastomosis was considered objectionable and was used in only one of the five cases. In the rare case where it is necessary to bridge a gap, the authors felt that the use of a vein-lined

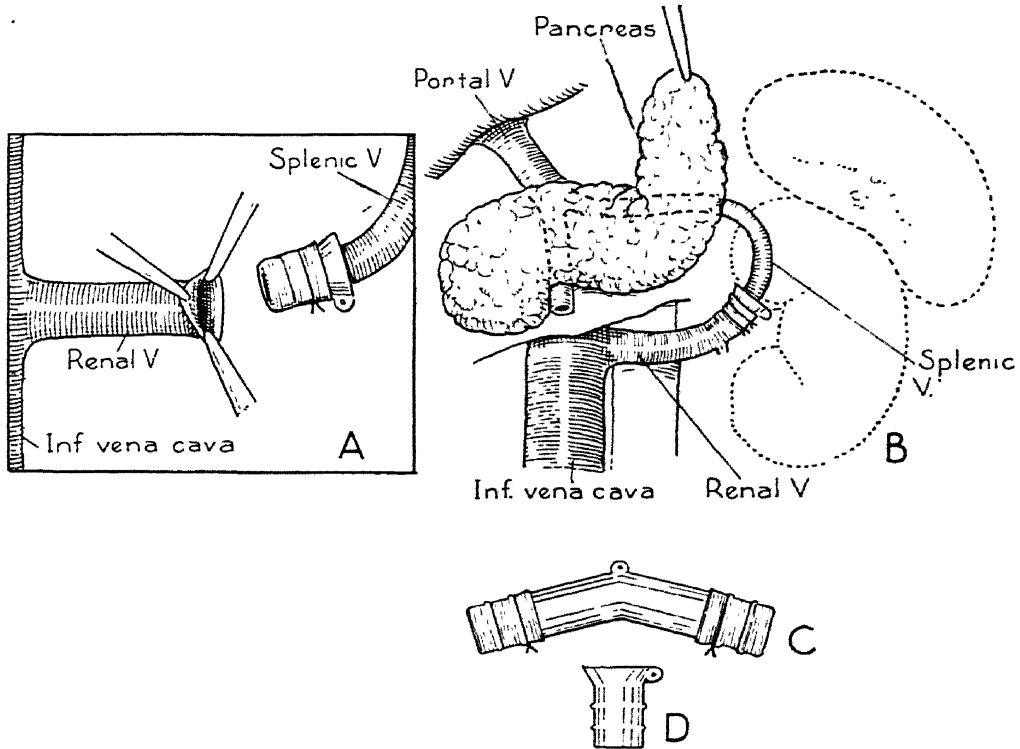


Fig. 2—*A*, Illustrating the method of everting the renal vein for the introduction of the vitallium tube bearing the splenic vein. The clamp on the flanged portion of the vitallium tube for its guidance and the rubber-shod clamps upon the splenic and renal veins have been omitted. *B* is a semidiagrammatic sketch of the completed anastomosis. Note the placement of the ligatures upon the vitallium tube. *C*, A vitallium tube with a vein graft mounted. *D*, An improved design of vitallium tube for end-to-end or end-to-side splenorenal anastomosis. There are two tying ridges placed 2 and 4 mm., respectively, from the end. Note the tab on the flange for the application of a holding clamp. (Blakemore, A. H. and Lord, J. W., Jr.: *Ann. Surg.* 122: 479 (Oct.) 1945.)

should be dissected back from the kidney for a distance of 5 or 6 cm. A rubber-shod clamp is then applied as far proximally as possible, and the vein divided as close to the kidney as possible, irrigating the lumen. The end of the splenic vein is then passed through the tube triangulated with mosquito clamp, everted (cuffed) over the end of the tube. The vein is held in place by a No. 1 silk suture behind the holding ridge. The renal vein is then triangulated with mosquito clamps and the intimal-

vitallium tube was preferable to a free-vein graft.

The Eck fistula type of portacaval shunt has an estimated blood-carrying capacity 30 to 40 per cent greater than the splenorenal anastomosis. In order to avoid the use of a vein graft; the portal vein is mobilized from its bifurcation at the liver to the origin of the splenic vein. The duodenum should be mobilized and the portal vein approached after medial displacement of the duodenum. Dissection of the portal

vein is facilitated by the use of an umbilical tape or small Penrose tube producing general traction. The cystic vein is ligated with C silk, flush with the portal vein and clamped distally and cut. Pyloric vein may or may not have to be sectioned. A rubber-shod clamp is placed on the portal vein at the origin of the splenic vein. A silk transfixion suture is placed around the portal vein at its bifurcation close to the liver and transected a few millimeters distal to the ligature. It is necessary to avoid the hepatic

through a proper-sized vitallium tube. The end of the vein is triangulated with mosquito clamps and the tube is held firmly by a clamp, the end of the portal vein is everted or cuffed over the end of the vitallium tube. The vein is held in place by a ligature tied tightly behind a holding ridge upon the tube, using a surgeon's knot. The vein-covered vitallium tube is now swung out from behind the common duct over the vena cava to the site selected for anastomosis. It is extremely important to avoid angulation

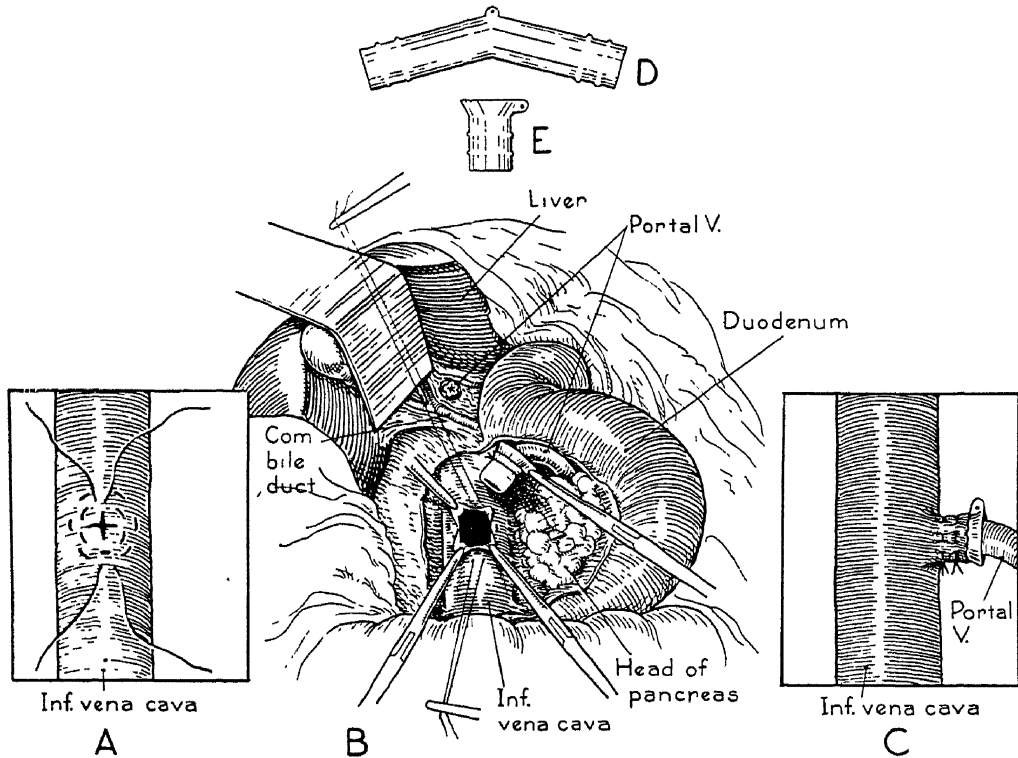


Fig. 3—A, Illustrating placement of the purse-strings in the vena cava and the centering of the cruciate incision for implantation of the vitallium tube bearing the portal vein. B shows the tube bearing the portal vein about to be introduced through the opening in the vena cava. C, The completed anastomosis. Note the vena cava wall is drawn well up on the vitallium tube. D, A tube suitable in design for vein graft bridging. E, A late design, double-ridge tube with a holding tab. (Blakemore, A. H. and Lord, J. W., Jr.: *Ann Surg.* 122: 481 (Oct.) 1945.)

artery and common bile duct during this dissection. The vena cava is mobilized by combined sharp and blunt dissection from the level of the liver down past the entrance of the left renal vein to the upper level of the right renal vein. The earlier passage of an umbilical tape about the vena cava with gentle traction facilitates dissection. The small venous branches are ligated with black silk. A rubber-shod clamp is placed about the vena cava at the upper level of the left renal vein but does not occlude the vessel. The portal vein is passed

or compression of the portal vein. A purse-string suture, 4 mm. larger than the diameter of the vitallium tube, is placed through all the layers of the vena cava. A second purse-string is placed 2 mm. outside of the first one. A second rubber-shod clamp is placed about the vena cava as close to the liver as possible. The distal rubber-shod clamp is now quickly tightened to completely occlude the vena cava at the level of the left renal vein recording the time of occlusion. A cruciate incision not exceeding in length the diameter of the vitallium

tube, exactly centered within the purse-string area, is made. The vitallium tube bearing the portal vein is grasped with the clamp and advanced through the opening into the vena cava against steady countertraction upon mosquito clamps. The purse-string sutures are then tied, completing the anastomosis. The rubber-shod clamps are removed from the vena cava and then from the portal vein, hemostasis obtained, and the abdomen closed carefully in layers. The external iliac vein may be used for a graft if necessary, since this more closely approximates the diameter of the portal.

There were ten cases subjected to portacaval shunt—five of the splenorenal type and five of the portal vein to vena cava. The portal pressures observed in the authors' cases varied from 260 mm. of water to over 500 mm. of water. This is markedly increased from the normal of about 8 mm. of mercury. Increased pressure is a potent factor in maintaining the patency of an anastomosed vein. The rate of blood flow is extremely increased. It is pointed out that this gives you accurate intima-to-intima coaptation without deposition of a foreign body in contact with the circulating blood, which is an advantageous factor in any blood vessel anastomosis.

Blakemore and Lord<sup>20</sup> point out that a common cause of portal hypertension is obstruction to the flow of portal blood through the liver caused by Laennec's cirrhosis. With Banti's disease, the obstruction may be in the portal or splenic veins. In five cases, a portacaval shunt was performed for relief of portal hypertension, using the nonsuture method of anastomosis over a single vitallium tube. Three of these were reported in some detail, the remaining two were considered too recent to have any follow-up significance.

A five-year-old girl, who was kept alive by continuous blood transfusions during an episode of bleeding from esophageal varices secondary to portal

cirrhosis, was subjected to an operation July 26, 1943. Following splenectomy and a left nephrectomy, the splenic vein and the left renal vein were anastomosed over a vitallium tube. At operation, the liver was found to be decidedly cirrhotic, the spleen was enlarged eight to ten times, and the left kidney showed early polycystic changes. For a few days postoperatively, the child suffered from distention and elevation of blood urea nitrogen associated with oliguria but improvement occurred on the fifth postoperative day and convalescence was uneventful. Seven months after operation the child had gained four pounds and her activities were normal. There was no recurrence of the ascites, the collateral abdominal veins had receded, and there was no evidence of occult blood in the stools. A urinalysis showed many hyaline casts, a few red and white blood cells, a specific gravity of 1.009 and a faint trace of albumin. The nonprotein nitrogen was 42.9 mg. per 100 cc., the urea ratio 50.6. Phenolsulfonphthalein excretion was 50 per cent. Fourteen months after the operation, the child showed evidence of anemia and passed three tarry stools. She was given multiple transfusions for eight days and the hemoglobin rose from 50 per cent to 82 per cent. The liver remained enlarged, there was no ascites, the nonprotein nitrogen level fell from 90 to 47.9 during this period of hospitalization. Seventeen months after the operation, the child was active and went to school.

A girl, age fifteen, who had suffered from repeated massive hemorrhages into the gastrointestinal tract since the age of four with relief of the splenomegaly following each episode of bleeding, was also subjected to splenectomy and left nephrectomy with anastomosis of the renal and splenic veins. The liver was found normal in the case. Pressure in a

branch of the coronary vein before anastomosis fell from 310 mm. of mercury to 190 mm. of mercury following the anastomosis. Her postoperative course was uneventful, five months after operation showing a gain of ten pounds in weight without any recurrence of bleeding.

The third case was a white male, age thirty-eight, who was suffering from portal hypertension due to cirrhosis of the liver. A splenorenal anastomosis using an 8-mm. vitallium tube was performed. Five months after this operation, the patient felt well, there was no ascites, the cephalin flocculation test had returned to normal.

The authors felt that while insufficient time had elapsed to adequately judge these few cases, the present knowledge would indicate that further trial was warranted. They did not feel that the bleeding which occurred in the first case was due to a blockage of the portacaval shunt. The lateral vessels may have been overtaxed at that time due to the effects of nitrogen retention on blood pressure. It is important to establish the exact renal status before operation and study the information gained from measuring the portal pressure and venography at operation. It was suggested that splenectomy as a therapeutic measure for congested splenomegaly should be limited to those cases in which the obstruction is in the splenic vein and at a point distal to the origin of the coronary vein.

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## JAUNDICE

Eiss<sup>1</sup> points out that in so-called surgical (obstructive) jaundice there is usually a history of biliary colic and this is the most important factor pointing to a surgical condition. The history of chills, fever, and light-colored stools may also be obtained. Tenderness and rigidity of the upper quadrant may or may not be present.

It is not always possible to select cases for operation on the basis of history or physical examination alone. Laboratory tests based on disturbances of normal functions of the liver are often helpful in establishing the diagnosis. The tests are grouped under: (1) Secretion of bile, bile and urobilinogen in the urine, icteric index of blood, Van den Bergh tests of blood; (2) storage of carbohydrate—galactose tolerance tests; (3) excretion or secretion of enzymes—phosphatase in blood; (4) detoxifying—formation of hippuric acid from sodium benozate; (5) abnormal globulin forma-



tion—cephalin-cholesterol test; (6) dye excretion—bromsulfalein retention, and (7) storage of vitamin K and prothrombin formation—prothrombin level of the blood.

Even in the most acute surgical cases, a preliminary period of four to six hours' preparation with *saline*, *glucose*, and *water* and the administration of *vitamin K* along with *protein* in the form of plasma or amino acids is indicated. In the less acute case, salt, water, glucose, vitamin K, and protein may clean up a jaundice due to poisons or cirrhosis. The laboratory tests may not differentiate between obstruction, cirrhosis, stone in the common duct, liver abscess, metastases to the liver, or carcinoma of the common duct or head of the pancreas. The presence of persistent signs of obstructive jaundice demands surgical exploration.

It is pointed out by Bradley *et al.*<sup>2</sup> that the occurrence of jaundice in man after administration of human blood products (plasma and serum) is now a well recognized phenomenon. This "homologous-serum jaundice," which is of hepatic origin, is readily distinguished from the hemolytic icterus which may arise immediately after transfusion with incompatible blood, or out-of-date stored blood. Clinically, it is similar to, if not indistinguishable from, epidemic hepatitis (catarrhal jaundice), but the incubation period is unusually long—commonly two to three months, in contradistinction to the twenty- to forty-day period believed to occur in epidemic hepatitis.

A high incidence (57 per cent) of this jaundice has been observed by the authors among seventy-one subjects during the course of an investigation into allergic reactions to human serum. All of these subjects received full human serum from a single batch; a few of them received in addition whole blood or serum from other batches. This batch

was distinguished by the common factor of icterogenicity which was confirmed by deliberately administering this batch to four volunteer patients with rheumatoid arthritis in whom it was desired to produce jaundice for therapeutic reasons.

The dose of homologous serum varied from 0.1 to 1200 cc. The attack rate was about the same whether the serum was given intradermally or intravenously and whether it had been given in a large single dose or repeated doses. The severity of the hepatitis appeared to be unrelated to the size, the route, or the frequency of the injection. The latent period seemed shorter when given in larger or repeated doses. No evidence of permanent liver damage was discovered. The incidence of jaundice was no greater in the allergic than in normal controlled subjects.

When the syndrome occurs after inoculation of measles convalescent serum, or yellow fever vaccine, it is relatively easy to detect icterogenic batches of material, because in most instances serum from only a single batch has been given. When jaundice follows transfusion, it may be impossible to decide which is the causative batch because in the usual transfusion practice several batches of plasma or serum may be administered to a single patient and not infrequently whole blood is given as well. It was impossible to determine the icterogenic batches of serum or plasma by the usual laboratory or animal experiments, and accurate records of the blood products given to patients with careful follow-up for several months afterwards is necessary in order to determine this property.

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## PANCREAS

FREDERICK A. FISKE, B.S., M.D., F.A.C.S.

## Physiology

According to Miller and Wiper,<sup>1</sup> physiological observations on patients with external pancreatic fistula have been extremely rare. Most of the investigations have been on experimental animals. They reported observations on:

1. The general nutritional state of the patient.
2. The total pancreatic flow in twenty-four hours.
3. The pattern of flow in a twenty-four-hour period.
4. The plasma-electrolyte pattern.
5. The plasma protein.
6. The influence of water intake on the pancreatic flow.
7. The observations on volume-flow alterations induced by the administration of various substances into the duodenum.
8. The effect of intravenous fluids upon the pancreatic secretion.
9. Observations on volume-flow alterations induced by the subcutaneous administrations of drugs.

Detailed statistics are presented.

It was found that pancreatic flow is continuous throughout the twenty-four-hour period and is influenced to a great degree by the state of hydration of the individual. One pancreas produced 1770 cc. of fluid in twenty-four hours. There was a marked alteration in the water balance, plasma-protein level, and plasma electrolytes, especially plasma sodium in patients with severe external pancreatic fistula. This loss of plasma sodium may produce a clinical syndrome similar to that described by Addison with the exception that adrenal disease is not present. The analogy has not been emphasized previously. Adequate amounts of *sodium* and *water* in the presence of sufficient plasma protein to hold them in

circulation alleviate the symptoms of this syndrome.

Pancreatic secretion may be diminished by a number of drugs, *ephedrine* and *sodium bicarbonate* are the most practical because they lack the unpleasant and deleterious side effects of others. *Histamine*, *physiological saline solution*, or 5 per cent *glucose* in physiological saline solution intravenously, stimulates pancreatic secretion.

The physiological observations which contribute definite support to the theory that secretin secretion is a filtration process are:

1. Sodium ion is present in equal amounts in both blood plasma and pancreatic secretion.
2. The total of the concentrations of chloride and bicarbonate ions are the same in blood plasma and pancreatic secretion.
3. The same amount of ionizable calcium is present in blood plasma and pancreatic secretion.
4. Sulfanilamide is found in the same amount in blood plasma and pancreatic secretion.

It was pointed out that large amounts of ionizable calcium are returned to the gastrointestinal tract normally through pancreatic secretion. The appearance of *sulfanilamide* in a therapeutic concentration in pancreatic secretion suggests its use in the treatment of acute inflammatory disease of the pancreas.

## Serum Enzymes

The relative diagnostic value of serum amylase and serum lipase in patients with diseases of the pancreas, liver, and gallbladder was compared by McCall and Reinhold.<sup>2</sup> One hundred and twenty-two consecutive serum amylase determinations in 104 patients and 165 consecutive serum lipase determinations in 135 patients provided the basis for this

study. In sixty-one cases, both enzyme tests were performed. Serum lipase was determined by the method of Crandall and Cherry. The serum amylase was determined by the method of Somogyi modified by substitution of the Folin blood sugar determination. This was found to give somewhat lower results than the original, due to greater specificity of the Folin reagent. The results were expressed as reducing substances liberated per 100 cc. of serum. Lipase values are expressed as the cubic centimeter of one-twentieth normal sodium hydroxide required to neutralize the fatty acid liberated by 1 cc. of serum from the olive oil substrate during twenty-four hours' incubation at 100.4° F. (38° C.). The normal serum lipase does not exceed 1.5 cc. of one-twentieth normal sodium hydroxide per cc. of serum. The normal range of serum amylase when modified was found to be 62 mm. per 100 cc. with a standard deviation of 13 mg. The range was thus from 36 mg. to 88 mg. The serum lipase was over 1.5 cc. in twelve of thirteen cases of acute pancreatitis. All of the nine cases tested showed an amylase over 100 mg. and eight of these showed values over 200 mg. Fifty-five per cent of these results were checked either by operation or autopsy. Serum amylase determinations were performed in seven cases and serum lipase in sixteen cases of carcinoma of the head of the pancreas. Serum amylase was elevated in only one case, while nine showed elevation of the lipase value. It was therefore suggested that a high lipase, together with a normal amylase in the presence of painless jaundice, is strongly suggestive of the diagnosis of carcinoma of the head of the pancreas. An elevated serum lipase of 2.2 cc. was found in one case of pancreatic calculus

with diabetes mellitus. Serum amylase was elevated in three of five cases. These were pancreatic abscesses (125 mg.), pancreatic cysts (280 mg.), and metastatic carcinoma from the breast (331 mg.).

In ten cases of portal cirrhosis of the liver, amylase was below 100 mg. Six of these were under 50 mg. and four below 30 mg. The serum lipase was low in all of these cases. However, this was also the case in other diseases of the liver studied and it was not thought to be significant.

Fifteen cases of chronic calculous cholecystitis, nine of whom had common duct stones, were studied in the lipase group and seventeen cases in the amylase group, six of which had common duct stones. As a result of these studies, it appeared that serum enzyme activity in cases of calculous common duct obstruction is increased only in cases in which the pancreas has been damaged. The serum enzyme tests were also performed in sixty-six cases with diseases other than those discussed. Elevated values were observed in four of the thirty-seven cases in the lipase group and seven of the twenty-nine cases in the amylase group. It was surmised that these cases showing elevated enzyme activity had associated pancreatic disease but there was no definite proof of this fact.

Correlation between serum amylase and lipase activity was not as close as the authors anticipated. A coefficient of correlation for the entire group was 0.66. Therefore, it was felt that the value of both tests is increased when they are performed on the same patient. It was pointed out that both tests could be performed easily but the serum amylase was most useful clinically because of the rapidity with which it could be performed.

### Fibrocystic Disease

Philipsborn *et al.*<sup>3</sup> point out that fibrocystic diseases of the pancreas and celiac disease are difficult to differentiate. Fibrocystic disease is characterized by an achylia or hypochylia pancreatica. Since the stools in celiac and fibrocystic disease may be identical, and the vitamin A curve is not diagnostic, a qualitative analysis of the duodenal drainage for enzymatic activity, coupled with a notation of the response of the pancreas to secretin or intraduodenal hydrochloric acid, is the most reliable laboratory aid in a differential diagnosis. Permanent pancreatic insufficiency with infantilism must be differentiated from celiac disease, fibrocystic disease, and certain types of feeding problems. The value of cryptic activity is the most reliable index of pancreatic function. Values of less than 4 gm. of liberated nitrogen per 100 cc. of duodenal fluid are abnormal in children. Less than 0.5 gm. of liberated dextrose per 100 cc. during the first twelve months is abnormal. Subsequently, less than 2 gm. of liberated dextrose is abnormal in children. When less than 60 cc. of one-twentieth normal sodium hydroxide is required to neutralize the free fatty acids produced by the lipolytic activity of 100 cc. of duodenal fluid, the pancreatic lipase may be considered diminished in children. The enzymatic activity in duodenal drainage is greatly diminished in fibrocystic disease, while it remains normal in celiac disease. The response to intravenous secretin or intraduodenal one-tenth normal hydrochloric acid is reduced in fibrocystic disease but may remain normal in celiac disease and in transient or permanent hypochylia pancreatica.

### Cysts

It was felt by Pinkham<sup>4</sup> that since no valid differentiation can be made be-

tween "hematic" cysts (pseudocysts) and necrotic suppurations, one should refer to them simply as collections secondary to pancreatic trauma, inflammation, or necrosis. The term retention cyst should be used to designate cystic dilatation arising secondarily to partial or complete occlusion of the pancreatic ducts. True cysts should be limited to denote those of proliferative (neoplastic, hydatid, or congenital origin). He reported a series of ten cases of pancreatic accumulations, six of these following acute pancreatitis and pancreatic necrosis. Biliary tract disease was associated in four cases, while in one no mention was made of the biliary tract and in the other it appeared normal. Two cases developed subsequent to suppurative pancreatitis; the first resulted from septic hemorrhagic pancreatitis and the second appeared to be one of acute and chronic pancreatitis with partial obstruction of the pancreatic duct. The other two cases presented followed chronic pancreatitis. Both of these patients had long histories of repeated episodes of epigastric and abdominal pain suggesting chronic pancreatitis. In one of the cases, dilatation followed obstruction of the duct and in the other pancreatic calcifications were found. Cultures taken in seven of these cases showed bacterial growths in four, two contained *Bacillus coli*, one *Bacillus subtilis*, and one *Staphylococcus albus*. Fat necrosis was found at operation in all but one of the cases, although a lapse of several weeks between the onset of the disease and the time of the operation occurred. Serum amylase and amylase determinations of the contents of the cyst were studied in six cases. The serum amylase dropped following drainage of the cyst in four cases, whereas in two cases it remained elevated above normal for several weeks. There was apparently no relationship

between serum amylase and the amylase content of the cystic fluid. Although chronic pancreatitis is not always associated with an increased serum amylase, an elevation of this is suggestive of the presence of a pancreatic collection. Further observations of this effect should be conducted and it is possible that this may be an early diagnostic aid. Rupture of these accumulations is said to be fatal, although it is very rare. It occurred in one of the patients who recovered after a stormy convalescence. Satisfactory results were obtained in all of the cases reported by single drainage or marsupialization of the pancreatic collection. Symptoms were not specific, consisting of prolonged indigestion, abdominal discomfort, in some instances following an acute episode of upper abdominal pain. It is difficult to differentiate this condition from gallbladder disease or peptic ulcer with its complication. The presence of a mass may be helpful in differentiating the two conditions. This may be demonstrated either by roentgenogram or abdominal palpation. The serum amylase test may be suggestive and of some diagnostic value. The coexistence of biliary tract disease is not uncommon and this possibility should be investigated at the time of operation. Sudden enlargement of the cysts with shock and intense pain suggests a massive hemorrhage into the cyst. Sudden decrease in the size of a cyst associated with diarrhea, shock, and a rigid abdomen may follow rupture of the cyst contents into the bowel or free peritoneal cavity. Many of these smaller cysts and accumulations often spontaneously subside and escape clinical detection. Gastric pneumograms were found to be of material aid in the roentgenologic diagnosis of retrogastric and pancreatic enlargements. Cysts may be visualized on flat plates, barium may show displacement of the stomach by the

mass, the duodenal loop may be widened due to enlargement of the head of the pancreas, and the pneumogram, demonstrating irregularity or enlargement in the retrogastric tissue, is of considerable diagnostic value.

### Trauma

Keynes<sup>5</sup> reported two cases of rupture of the pancreas and its duct occurring in young soldiers. In the beginning, both were uncomplicated but later one patient developed a persistent fistula and, during the postoperative course, both had complications. Recovery occurred in both patients. The second case was of particular interest because the rupture occurred as a result of an underwater blast and this is thought to be the only example of its kind described.

The first patient, aged twenty, was injured while riding a bicycle and colliding with a broom placed across a runway. He was struck in the epigastric region and shortly after developed signs of acute abdominal crisis. Immediate operation revealed a rupture of the body of the pancreas over the vertebral column. There was no other visceral injury. Drainage was immediately established, the fistula healed spontaneously, but three months later a large pseudocyst formed. This lesion was opened and drained.

The lipiodol injection of the fistula indicated that the duct of Wirsung had been ruptured, the lipiodol entered the left two thirds of the duct but could not be seen entering the right one third. The fistula was implanted into the jejunum. For several months after operation, the patient experienced attacks of abdominal disturbance but during the subsequent six months there was no symptom.

The second patient, aged twenty-two, crashed from a plane at sea. Following this, he was perfectly normal, having

floated upright in the water, supported by a life belt. A "U" boat explosion at a distance of about 400 yards produced a peculiar sensation in the abdomen which was described as "a rumbling in the belly." Operation was performed about nineteen hours after the blast. Free blood in the peritoneal cavity and a tear in the peritoneum on the outer side of the hepatic flexure of the colon with retroperitoneal hemorrhage was discovered. The retroperitoneal space was drained through a stab wound in the loin, the colon was sutured into place, and the abdomen was closed. On the tenth day he developed a large swelling in the epigastrium which was regarded as a pseudocyst of the pancreas. The following day signs of acute intestinal obstruction developed. A second laparotomy was performed and the lesser peritoneal sac was opened through the gastrocolic ligament. About three pints of muddy fluid were evacuated and a vertical tear through the middle of the body of the pancreas was discovered. Ten days later a third laparotomy was performed for signs of acute intestinal obstruction. This revealed a volvulus of the small intestines which was reduced and the abdomen was closed. Drainage from the lesser peritoneal sac ceased about seventeen days after the second laparotomy. The patient had to undergo a fourth operation for repair of a large ventral incisional hernia. There were no further complications and he returned to full duty, two months later.

A case of forcible compression of the upper abdomen for several seconds is reported by Curr.<sup>6</sup> The patient walked to the hospital where upper abdominal pain and rigidity were observed in exploratory laparotomy six hours after injury. At operation a large amount of fresh blood was found in the peritoneum. A three-inch tear was found in the trans-

verse mesocolon with severe bleeding of a branch of the middle colic artery. The pancreas was vertically split into two parts, approximately through the center, with a gap of fully two inches. Due to the wide separation, it was impossible to carry out an end-to-end union, so several deep mattress sutures were used to close the raw surfaces. The splenic vein which was cut was ligated, a large gauze was inserted and wound closed.

A pancreatic fistula developed which closed in nine weeks. Drainage decreased on low protein diet and increased on ordinary diet. There was considerable weight loss during the nine weeks but after closure of the fistula, weight returned to normal in six weeks. A small incisional hernia was the only final disability.

### Pancreatitis

The importance of the serum amylase test in the differential diagnosis of pancreatitis was emphasized by Morton.<sup>7</sup> The possibility of this condition must always be fully considered in patients complaining of sudden severe epigastric pain. The test is easily performed accurately and gives important information in the diagnosis of these cases. Clinically, there are two distinct pathological types of pancreatitis recognized — the acute edematous and pancreatic necrosis. Acute edematous pancreatitis can be diagnosed by the serum amylase test and the rapid clinical improvement under conservative treatment. The pancreatic necrosis is often prostrating from the beginning. The serum amylase values may or may not be elevated and the patient fails to show improvement. Conservative treatment of pancreatic necrosis or pancreatic abscess is not advisable. If either condition is suspected, operation should be performed at once. After the acute edematous pancreatitis has sub-

sided, biliary tract surgery consisting of exploration of the common duct and dilatation of the sphincter of Oddi is indicated and should be followed. The author did not advocate drainage of the common duct in all cases. This was dependent upon the amount of infection present and he often closed the common duct without drainage. The operation advocated in acute pancreatic necrosis was simple drainage either through the foramen of Winslow or through the gastrocolic or gastrohepatic omentum. If an obstruction to the common duct is discovered, this should also be relieved. It is pointed out that surgical manipulation around the lower end of the common duct or the head of the pancreas may be followed by postoperative acute pancreatic edema. This may often be demonstrated by a blood amylase determination. Resection of a posterior duodenal ulcer perforating into the pancreas may also precipitate an attack of acute pancreatitis.

Shallow *et al.*<sup>8</sup> report twelve cases of acute pancreatitis observed in a two-year period. There was an equal number of the edematous and hemorrhagic type of lesions. In the entire series there was one death—there were no operative deaths which they attributed to delayed surgery or conservative surgery. It was pointed out that the exact etiology was still undetermined, the usual view being that it is due to the reflux of infected bile into the pancreatic ducts. A third view is partial obstruction to the outflow of pancreatic secretion due to metaplasia of the epithelium of the branches of the pancreatic duct, and others believe acute pancreatitis results from a circulatory disturbance in the pancreas. It is not well understood how the enzymes become activated. Trypsin leads to digestion of the pancreas with necrosis and rupture of blood vessels within the gland

followed by hemorrhage. The liberation of lipase is also an important feature of the disease and produces fat necrosis. The profound shock may be explained on the basis of absorption of split protein products or of trypsin itself.

The diagnosis on clinical signs alone is often difficult and a serum amylase test should be done. This test is practically specific for the lesion and seldom if ever gives false positive reaction.

The authors felt that once a diagnosis was established, operation should be delayed and perhaps not performed at all. If the diagnosis is established at the time of operation, only those conservative measures aimed at correcting the contributing pathology should be done. Extensive surgery of the pancreas itself should be avoided.

It is pointed out by Shallow *et al.*<sup>9</sup> that while conservative nonoperative management of acute pancreatitis has been stressed in the literature, surgical intervention is indicated in the presence of abscess formation. They present a case of acute hemorrhagic pancreatitis followed by bacterial invasion, involvement of the pancreatic vein, and perhaps the splenic vein by infection, and feeding of bacteria or septic emboli into the liver through the portal vein. It was thought that the infection from the pancreas to the liver may have occurred *via* the lymphatics. A normal serum amylase on the sixth day, following the onset of the attack, is in keeping with cases reported in the literature and also the authors' experience. The level usually falls within twelve to seventy-two hours after the onset of the attack. Biliary tract disease was absent in this case, which is an unusual finding, since 70 per cent of the cases are associated with lesions of the biliary tract. The jaundice was thought to be of hepatic origin and perhaps to a lesser degree from compres-

sion of the common bile duct due to transient edema of the pancreas. A hematogenous pancreatic abscess was thought unlikely in this case. It was pointed out that serum calcium findings below 9 mg. per 100 cc. of blood usually occur in cases of pancreatic necrosis sometimes between the second and fifteenth day of the disease, and that values below 7 mg. indicate a fatal prognosis. In this case, a serum calcium of 9.2 was found on the fourteenth day of the disease. Diabetes mellitus did not follow in this case. According to Allen, destruction of seven eighths of the gland or more is necessary to induce a diabetic state.

The patient was a 55-year-old female with a chief complaint of epigastric and right upper abdominal pain of three days' duration. The pain was constant, did not radiate, was accompanied by nausea and vomiting of greenish-yellow material. There was an associated diarrhea with the passage of four loose stools daily for two days. There was nothing in the past history to suggest biliary tract disease. Physical examination showed a moderately obese Italian woman, extremely apprehensive, slightly irrational, and acutely ill. Temperature, 103°, pulse 130, respiration 26, blood pressure 140/90. There was slight jaundice and marked dehydration. The abdomen was slightly distended and abdominal respiratory motion restricted. Exquisite tenderness, marked rigidity, and rebound tenderness in the upper right quadrant. No masses palpable, hemoglobin 78, red blood cells 4,000,000, white blood cells 13,600 with 57 per cent polys (8 per cent young forms), lymphocytes 39 per cent, monocytes 3 per cent, and basophils 1 per cent. Urinalysis slight albuminuria, Wassermann and Kahn negative, blood urea nitrogen 9 mg., sugar 114 mg., serum protein 6.5 gm. Van den Bergh's direct positive with serum bilirubin of 2.1 mg. Bromsulfalein liver function studies, 20 per cent dye retention. Prothrombin time, 68 per cent of average normal. Blood culture, no growths in forty-eight hours. Negative flat plate of the abdomen.

The patient was treated by a modification of the Ochsner method for three days without improvement. At this time a mass became palpable

in the right upper quadrant. On the fourth day, the patient developed respiratory difficulty, an increase in the leukocyte count to 18,000 on the third day, 20,000 on the fourth day, and 26,000 on the fifth day. Five gm. of *sodium sulfadiazine*, which had been given daily from the time of admission, was discontinued and *penicillin* administered intramuscularly at two-hour intervals.

Operation under pontocaine spinal anesthesia on the sixth day revealed a normal gallbladder and biliary tract, no evidence of perforation of the stomach or duodenum, marked congestion, edema, and fat necrosis of the gastrohepatic omentum and a boggy mass protruding into the lesser peritoneal cavity. Fat necrosis was also present in the gastrocolic omentum. The lesser peritoneal cavity was exposed through the gastrohepatic omentum. This revealed a fluctuant mass within the pancreas, containing about eight ounces of extremely foul-smelling material, with some necrotic pancreatic tissue, which on culture showed gram-positive cocci due to *Streptococcus haemolyticus*. The quadrant lobe of the liver, on the inferior surface between the falciform ligament and the gallbladder, presented a slight bulge suggesting an underlying abscess. An aspirating needle was introduced and 5 cc. of pus readily obtained. The liver was incised over this area and a finger introduced. Two abscess cavities in direct communication were palpated, four ounces of foul, thick, creamy, yellow material aspirated which also showed *Streptococcus haemolyticus* on culture. This abscess was not in continuity or contiguity with the one in the pancreas. Two iodoform packs and a Penrose drain were inserted into the abscess cavity of each organ and an additional Penrose drain into the right kidney pouch. These were brought out through the upper pole of the wound which was closed in layers. During the first week the patient drained profusely, requiring several changes of dressings daily. The jaundice subsided, the temperature and pulse gradually decreased, and the patient's mental state improved. The drains were started out on the seventh day and completely removed by the tenth. Jaundice had entirely subsided by the twentieth day and she was discharged thirty days following the operation with a slight amount of drainage from the wound. She was readmitted and treated twenty days after this admission for a wound infection due to *Streptococcus haemolyticus* and *Staphylococcus aureus*, which cleared up after fifteen days of treatment in the hospital. A



follow-up three months later showed that the patient had a good appetite, had gained ten pounds in weight, and was free of drainage or fever.

This case\* showed the importance of scrupulous pre- and postoperative care in a serious condition, which consisted of supportive measures, such as *fluids intravenously, plasma, blood, and vitamins; Wangensteen decompression*; chemotherapy with *sulfonamides* and *penicillin*. Due to the gram-positive cocci, the authors felt that the use of penicillin for one week was an important factor in the patient's recovery. It proves that suppurative pancreatitis associated with liver abscess is a grave but not hopeless condition.

Following death from electrical shock, little has been recorded regarding the condition of the pancreas. Glazer<sup>10</sup> examined three men who died immediately following electrical shock. The pancreas showed focal areas of hemorrhage and hyperemia in each case, and also focal areas of coagulation necrosis. In two, the changes occurred in the tail, the head and body being normal; in the other, the entire pancreas was involved.

It is suggested that minor pancreatic changes may give no immediate symptoms in shock not resulting in death, but later may cause pancreatic insufficiency.

### Accessory Pancreas

Young<sup>11</sup> reports a case of accessory pancreas complicated by acute necrosis. The patient was a thirty-six-year-old male who was suspected of having a perforated ulcer. Midepigastria pain of a stabbing type had been present for three weeks before he was seized with generalized severe abdominal pain associated with abdominal rigidity. Operation revealed a firm mass in the gastrohepatic omentum along the lesser curvature of the stomach, which was separate

from this organ. The mass was the size of a walnut, irregular, firm but not stony hard, and unconnected with any other structures. The lesser omental bursa was explored and found to be normal. The pancreas was not unduly hard or irregular. Biopsy showed pancreatic tissue with areas of necrosis.

### Adenoma of the Islands of Langerhans

The pathology of adenoma of the islands of Langerhans was reviewed by Good<sup>12</sup> in an attempt to show that the structure of the wall of the pancreatic duct and the wall of the capsule is the same, and therefore the capsule is the duct wall and its presence or absence depends upon whether the adenoma took origin in a duct with or without a wall. The theory of origin and a mature adenoma was abridged by showing the proliferation of the duct epithelium and intraductal islands of cells representing stages of growth. Excellent photomicrographs are presented. A schematic illustration based on a total of 163 cases of adenoma of the islands of Langerhans reporting the size and distribution of these is illustrated.

According to Brush and McClure,<sup>13</sup> functional hypoglycemia is fairly common, but organic hyperinsulinism is rather rare. It is extremely important to use every diagnostic possibility in order to properly evaluate a case of hypoglycemia. The Whipple triad (of symptoms) is a definite indication for surgical exploration of the pancreas. An islet tumor will be present in nearly all the cases. This includes:

1. Disorder of the nervous system, such as confusion, coma, convulsions, collapse coming on in the fasting state.
2. A drop in the blood sugar level to 50 mg. per 100 cc. or less.
3. The relief of symptoms brought about by the administration of glucose.

TABLE I  
ETIOLOGIC CLASSIFICATION OF SPONTANEOUS  
HYPOGLYCEMIA (*Conn*)

- 
- I. Organic—recognizable anatomic lesion:
1. Hyperinsulinism:
    - (a) Pancreatic island-cell carcinoma.
    - (b) Pancreatic island-cell adenoma.
    - (c) Generalized hypertrophy and hyperplasia of islands of Langerhans.
  2. Hepatic disease:
    - (a) Ascending infections—cholangitis.
    - (b) Toxic hepatitis.
    - (c) Diffuse carcinomatosis.
    - (d) Fatty degeneration or metamorphosis.
    - (e) Glycogenosis (von Gierke's disease).
  3. Pituitary hypofunction (anterior lobe):
    - (a) Destructive lesions (chromophilic tumors, cysts, etc.).
    - (b) Atrophy and degeneration (Simmond's disease.)
    - (c) Thyroid hypofunction—secondary to pituitary hypofunction.
  4. Adrenal hypofunction (cortex):
 

Atrophy or destruction of cortex.
  5. Central nervous system lesions (some interfere with nervous control of blood sugar).
- II. Functional—no recognized anatomic lesion:
1. Hyperinsulinism (autonomic nervous system imbalance).
  2. Renal glycosuria.
  3. Pregnancy and lactation.
- 

(Brush, B. E. and McClure, R. D : *Ann. Surg.* 120: 751 (Nov.) 1944.)

A blood sugar level over 50 mg. per 100 cc. during an attack indicates causes other than islet adenoma.

In cases where the blood sugar is above 50 mg. per 100 cc., a diet low in carbohydrate, 50 gm. or less, and high in protein will often relieve the attack. This is due to a slow conversion of the

protein, which will yield about 50 per cent dextrose, and also to a lower absorption rate, which prevents a sudden elevation of the blood sugar and stimulation of the pancreas. The glucose tolerance test is influenced by the preceding diet in normal persons as well as those suffering from hypoglycemia. Under proper conditions, this is an important diagnostic test in cases of hypoglycemia. Both the organic and functional hyperinsulinisms characteristically give a low dextrose tolerance curve, and the organic type usually has an abnormally low fasting level. In borderline cases, studies on the utilization of injected glucose are indicated. It was felt that a basal metabolic rate prior to the injection of glucose, and a repeat metabolism test at half-hour, one hour, two and one-half hours, and three hours after the injection were helpful. Urinary determinations for nitrogen and sugar were determined with proper carbohydrate, fat, and protein estimation. A calculation of the respiratory quotient gives diagnostic information and is of benefit in following the patient postoperatively. All of these studies aid in determining the advisability of performing a subtotal pancreatectomy in those cases not strictly conforming to the Whipple triad, and yet presenting symptoms of hyperinsulinism.

The first patient was a single white female, nineteen years of age, who complained of severe headache, abdominal cramps, chronic cough, and an excessive gain in weight. Roentgenograms of the chest and skull were both negative. A basal metabolism was minus five. The patient was taking 0.065 gm. (1 grain) of thyroid daily. Fasting blood sugars were 78 and 99 mg. per cent. Nine months later she complained of frequent attacks of weakness, sweating, tremor, and a stuporous mental reaction. These conditions were worse during the hunger

state and the injections of carbohydrate brought relief. Blood sugar levels during the attacks were from 55 to 60 mg. Routine laboratory examinations were negative and a clinical diagnosis of spontaneous hypoglycemia was made. At operation no tumor could be found and two thirds of the pancreas was removed. During the operation the patient received 400 cc. of *glucose* intravenously.

aged forty-three. She complained of nervousness, backache, low blood pressure, and sinus trouble. The first attacks of nervousness occurred in 1929 and were characterized by weakness, irritability, excessive perspiration, ravenous hunger, all occurring about three hours after meals and being worse after exercise. They were relieved by eating, especially readily available carbohydrates.

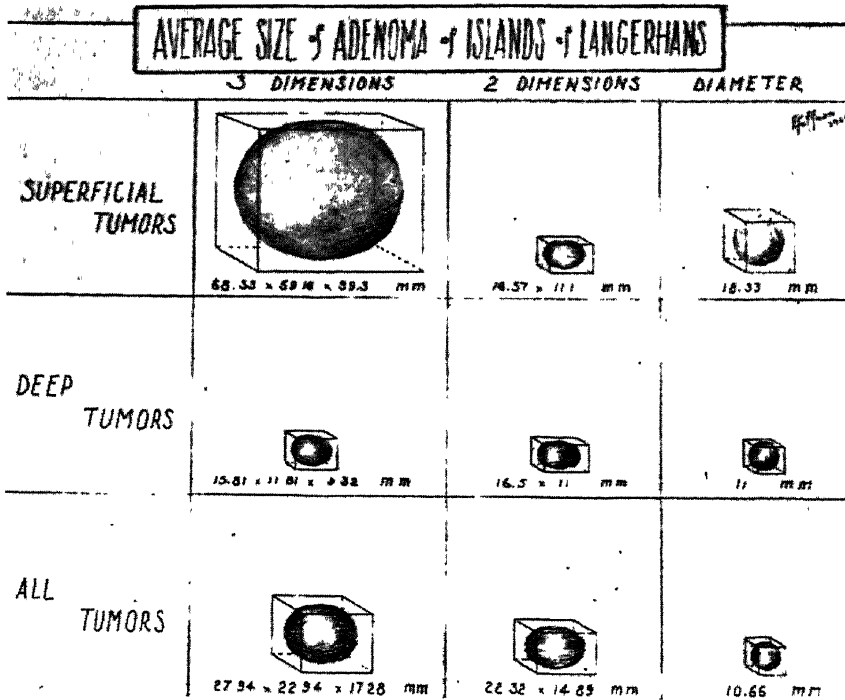


Fig. 1—Schematic representation of the average size of adenomas of the islands as reported in literature. Some authors gave measurements in three and some in two dimensions, some in diameter only. Averages for each method are recorded and drawn to scale. (Good, L. P.: Surgery 18: 168 (Aug.) 1945.)

and 500 cc. of *whole blood*. Hourly post-operative blood sugar determination showed 250, 230, 230, 170, and 140 mg. per cent. Daily blood sugar levels post-operatively showed 135, 129, 111, 129, 105, 104, 75, 93, 96, 84, and 89 mg. per cent. Postoperative course was uneventful and the patient remained asymptomatic with normal blood sugar tests at yearly intervals for about nine years.

The second case was more complicated—the patient was white, female,

There was a gradual loss in weight. The attacks became progressively more severe and a loss of memory during the attacks, mental cloudiness, speech difficulty, visual disturbances, and no loss of consciousness developed. Physical examination and routine laboratory tests were normal. Fasting blood sugar levels varied from 61 to 69 mg. per cent. Roentgenograms of the spine, skull, chest, gallbladder, stomach, and duodenum were normal. Strenuous exercise

during the fasting state would precipitate severe symptoms, with a blood sugar level of 60 mg. per cent at this time. One mg. of *epinephrine* subcutaneously relieved the symptoms within fifteen minutes, and a blood sugar at this time showed 73 mg. per cent. A high protein, low carbohydrate diet with five or six daily meals and thyroid extract, 0.33 gm. ( $\frac{1}{2}$  grain) daily, failed to relieve

Approximately five sixths of the gland was resected. Hourly blood sugar showed 108, 91, 85, 109, 127, 131, 145, 112, 132, and 98. A glucose tolerance test, twenty-four hours postoperatively with a phosphorus determination, is shown by means of a chart. Daily blood sugars varied from 80 to 100 mg. per cent. The post-operative convalescence was uneventful and the patient is enjoying excellent

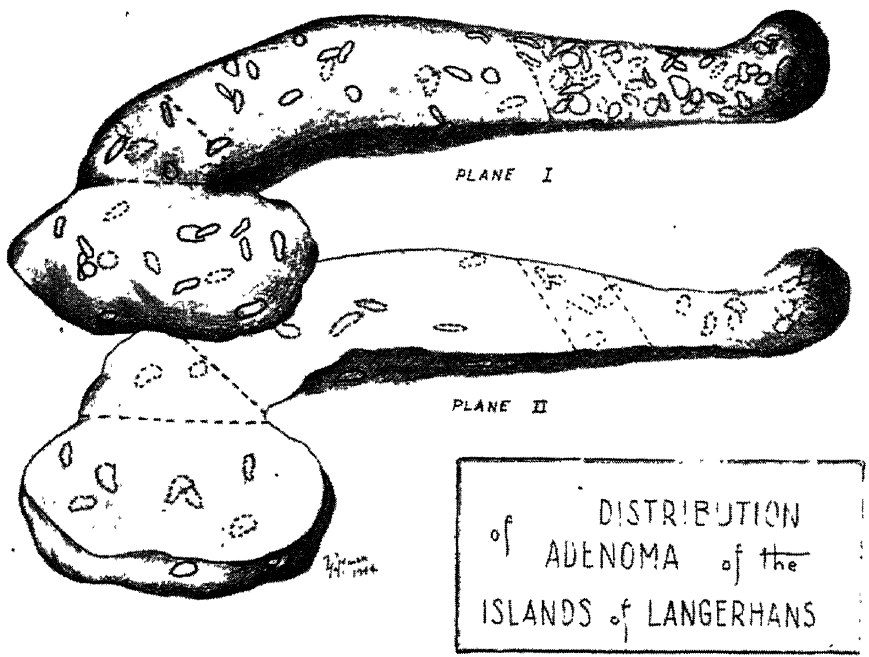


Fig. 2—Distribution of adenomas reported in the literature. The pancreas has been sectioned sagittally. The superficial tumors are represented in the anterior, the deep in the posterior, section. (Good, L. P.: *Surgery* 18:168 (Aug.) 1945.)

the symptoms and the patient was admitted to the hospital on two occasions at three-month intervals. In preparation for the operation, the patient received 500 cc. of 10 per cent *glucose* intravenously, which was followed by a reaction requiring 50 cc. of 50 per cent glucose for relief. During the operation she received 500 cc. of 10 per cent glucose and 500 cc. of *whole blood*. The tail of the pancreas was hyperplastic and firm but no adenoma could be found.

health without return of symptoms with fasting blood sugar levels varying between 80 and 100 mg. for approximately one year.

It is pointed out that excellent results may be obtained following subtotal pancreatectomy even in the absence of an adenomatous adenoma. The necessity of subtotal resection was emphasized, and it was pointed out that pancreatic function was not significantly affected when four fifths of the gland was removed.

The value of a *high protein, low carbohydrate diet* for a postoperative trial was emphasized. It was pointed out that hyperplasia of the islet cells is difficult to diagnose pathologically just as it is difficult to distinguish between benign and malignant tumors. Both of these cases showed a normal pathological report.

Two patients with hypoglycemia who were relieved of symptoms by surgical removal of an adenoma of the pancreas are reported by Walker and Boger.<sup>14</sup> It is stated that fifty-six cases of successful removal of benign adenomas of the islands of Langerhans have now been reported in the literature.

Hyperinsulinism should be considered, if only to be ruled out, in every neuropsychiatric case. Hyperinsulinism's relationship to the endocrine system is discussed, and the study it is believed will be furthered by greater attention to the alterations produced in the endocrine glands. The most effective therapy needed to prevent damage to the central nervous system as a result of long-standing hypoglycemia is surgical removal of these tumors.

The problem of islet cell tumors of the pancreas was briefly reviewed by Maxeiner and Bundy.<sup>15</sup> They emphasized the importance of being alert for a triad of symptoms described by Whipple consisting of attacks of insulin shock, coming on during fasting or an over-fatigued stage, blood sugar findings of 50 mm. per cent or less, and prompt relief by the ingestion of glucose. The nervous symptoms which occur consist of disturbance of the sympathetic system manifested by dizziness, nausea, pallor, and sweating, disturbance of the central nervous system manifested by convulsions with tonic or clonic contractions of the extremities and psychic disturbance consisting of anorexia, mani-

acal seizures, mental confusion, and coma. These attacks occur during fasting or overfatigue, when the blood sugar levels are abnormally low. The difficulty in making a diagnosis of hypoglycemia was pointed out and due consideration of thyroid, pituitary, and adrenal, as well as liver, must be completely evaluated in these cases. The value of subtotal pancreatectomy, in cases where surgical exploration fails to reveal by palpation or inspection an islet cell tumor, was considered advisable. A case was presented where nine islet tumors were found in the pancreas removed, although none of these could be demonstrated by inspection or palpation at the time of operation.

This patient was a twenty-four-year-old veteran suffering from attacks of unconsciousness, lethargy, drowsiness, and irritability associated with low blood sugars. Several times the patient went into a deep stupor and the blood sugar at this time was found to be 45 mm. per cent. After being A.W.O.L. for two days, he was brought to the hospital in a coma, at which time a blood sugar of 28 mm. per cent was found. Consciousness returned after the administration of glucose. Approximately 75 per cent of the pancreas was resected. There was marked clinical improvement following this operation, and the authors felt that due to personality changes and stabilization of blood sugar levels the patient was definitely cured of his disease.

### Carcinoma

**Ampulla and Head**—Whipple<sup>16</sup> advocates a one-stage removal of the head of the pancreas and duodenum with occlusion of the pancreas for these reasons:

1. The danger of hemorrhage and postoperative oozing is controlled by preoperative vitamin K therapy.

2. The danger of two anesthetics and two major procedures is thus avoided.

3. The difficulty of extensive and in some cases massive adhesions at the second and more difficult stage is avoided.

4. Continuous spinal anesthesia together with plasma and whole blood transfusions have made the one-stage procedure safer than the two-stage procedure. He performed a two-stage operation with a mortality of 38 per cent compared with nineteen one-stage operations with a postoperative mortality of 31 per cent. There was no mortality of the one-stage procedure for benign lesions.

5. In the one-stage procedure, two steps were considered important:

(a) The implanting of the common duct into the jejunum, either end-to-end or end-to-side, depending on the choice of the loop or Roux type of jejunojejunostomy. This avoids the danger of a cholecystoenterostomy and the serious complication of a biliary fistula as a result of the cutting through of a ligature on a ligated common duct.

(b) The implanting of the pancreatic duct into the jejunal loop below the choledochojejunostomy, which eliminates the uncertainty and debate regarding an occluded pancreas and possible fatty liver degeneration.

He states that provided a cholecysto-gastrostomy and ligation of the common duct is not done, there was little difference in what modification of the one-stage procedure was used. The author regrets that the two-stage procedure, as originally described, continues to be emphasized in the literature, since he condemns it at the present time due to improved methods of pre- and post-operative treatment. A one-stage choledochojejunostomy, with implantation of the pancreatic ducts into the jejunum, was advocated as the procedure of choice.

The case of a fifty-three-year-old woman complaining of epigastric pain, loss of weight and strength of two months' duration, with a history of three similar attacks twenty-three, twelve, and five years before, was reported. She weighed 80¼ pounds. Physical examination revealed a tired thin woman

who appeared chronically ill without anemia or jaundice. There was epigastric tenderness and a firm nontender, movable mass just above the umbilicus. R.B.C., 4,100,000; normal white and differential count. Gastric analysis: No free hydrochloric acid, 58 after histamine stimulation. Roentgen examination showed a large filling defect in the region of the palpable mass which suggested a penetrating ulcer. A diagnosis of carcinoma of the stomach was made and the patient transferred to surgery.

A partial gastrectomy, complete duodenectomy, removal of head and part of the pancreas, anterior gastroenterostomy—end-to-side, and a choledochoenterostomy were performed. Due to the mistaken diagnosis, the stomach was transected before inspecting the lesser peritoneal sac. The tumor mass was found occupying the head of the pancreas; it was hard, smooth, on underlying structures and not associated with enlarged lymph nodes. The section away from the portal vein and superior mesenteric vessels required skilful dissection and it was thought that invasion of these vessels would have occurred within a short period of two or three weeks.

The procedure followed was division of the vessels along the greater and lesser curvatures of the stomach. The transection of the stomach between Payr clamps, ligation of the gastroduodenal artery, division of the outer peritoneal reflexion of the duodenum, mobilization of the duodenum, and division of the branches of the inferior pancreaticoduodenal artery. The duodenum and jejunum were drawn to the right behind the superior mesenteric vessels and the duodenum cut with Payr clamps at the junction of the duodenum and jejunum. The distal end was sutured with an over-and-over stitch of No. 00000 chromic

and the stump buried with No. 1 silk mattress sutures. The head of the pancreas was dissected away from the portal and splenic vein and from the superior mesenteric vessel. The distal half of the stomach, all of the jejunum, and the head of the pancreas and the terminal portion of the common duct were then removed *en masse*. An antecolic gastrojejunostomy, end-to-side, was established between the stomach and the jejunum by open anastomosis; the cut end of the

insulinism or hypoglycemia could be demonstrated.

Difficulty encountered in making a diagnosis of carcinoma in the ampullary region at operation was pointed out by Orr.<sup>17</sup> Chronic pancreatitis or a benign adenoma may closely simulate carcinoma by palpation alone. A duodenotomy may reveal an impacted stone in the ampulla which can also be mistaken for a carcinoma. In all cases, a thorough exploration of the liver, head of pancreas, and

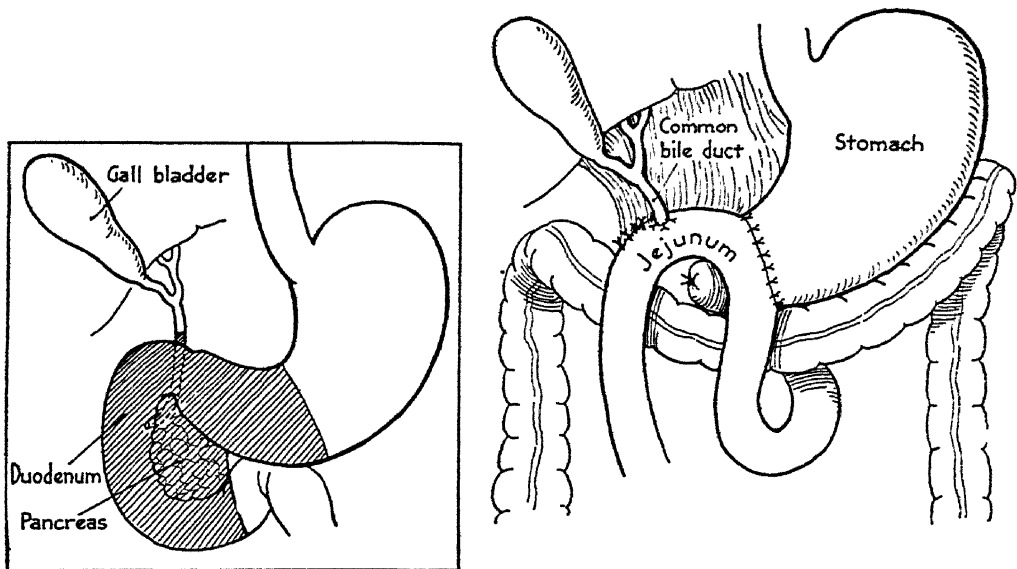


Fig. 3—One-stage radical pancreaticoduodenectomy with antecolic gastrojejunostomy and implantation of the common duct into the jejunum. (Whipple, A. O.: Ann. Surg. 121: 848 (June) 1945.)

common duct was anastomosed to the jejunum distal to the gastrojejunostomy. A Penrose drain was inserted to the head of the pancreas. A beginning carcinoma of the head of the pancreas of the islet-cell variety was found, in addition to a penetrating benign ulcer of the lesser curvature of the stomach. Convalescence was uneventful. There was a 30 to 50 per cent fat loss of the stools which was controlled by 5 panteric and 9 holadin tablets o.d. Her weight was maintained between 90 and 94 pounds and she was able to perform her usual duties as a clergyman's wife. No evidence of hyper-

regional lymph nodes should be made with biopsy of these or the papillary area of the duodenum exposed through a duodenotomy. If doubt still exists, the operative procedure should be divided into two stages.

Despite the discouraging results from pancreaticoduodenectomy, the operation is fundamentally sound and offers the best chance of cure in patients suffering from carcinoma of the ampulla or ampullary region. Accurate details of the final results of pancreaticoduodenectomy are incomplete and a careful study should be performed in order to determine the de-

gree of accuracy and the percentage of cures, as well as the average length of life following this operation.

Recorded evidence indicates that complete occlusion of the pancreatic ducts will result in fatty infiltration of the liver, reduction in fat and nitrogen absorption in most cases, and fibrosis of the pancreas with atrophy of the acinar tissue. Although there is abundant evi-

dence that patients and animals will live for several years, in comparatively good health with the external pancreatic secretion, there has been no valid reason why the severed pancreatic stump of pancreaticoduodenectomy should not be united to the intestinal tract. The preservation of the physiology of the pancreas is a very good reason for pancreatocenterostomy. The choice of a one- or two-stage

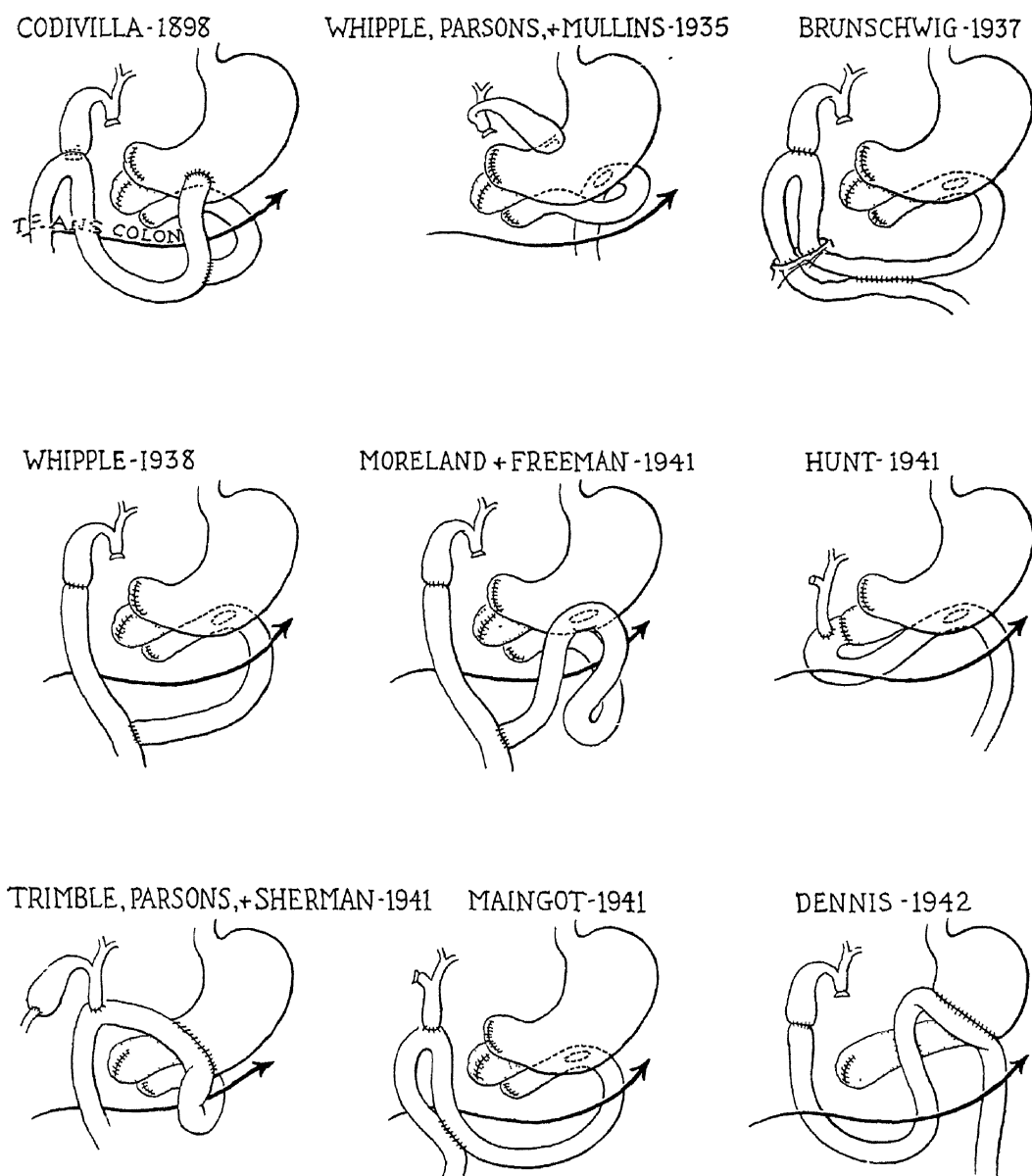


Fig. 4—Sketches illustrating various techniques of pancreaticoduodenectomy: Codivilla, Whipple, Parsons and Mullins, Brunschwig, Whipple, Moreland and Freeman, Hunt, Trimble, Parsons and Sherman, Maingot, and Dennis. (Orr, T. G.: *Surgery* 18: 154 (Aug.) 1945.)



operation must depend upon the general condition of the patient and the findings at the operating table.

A technic of pancreaticoduodenectomy should be adopted which will reduce the time of operation, minimize ascending infection of the gall tract, prevent pancreatic and biliary fistula, and preserve the normal physiology of digestion. The

various technics used by different surgeons is well illustrated in Figs. 1, 2, and the author's changes in technic in Fig. 3.

Eighteen patients were observed by the author: eleven of these had clinical evidence of metastasis, which brings up the question of what percentage of these patients is curable by successful

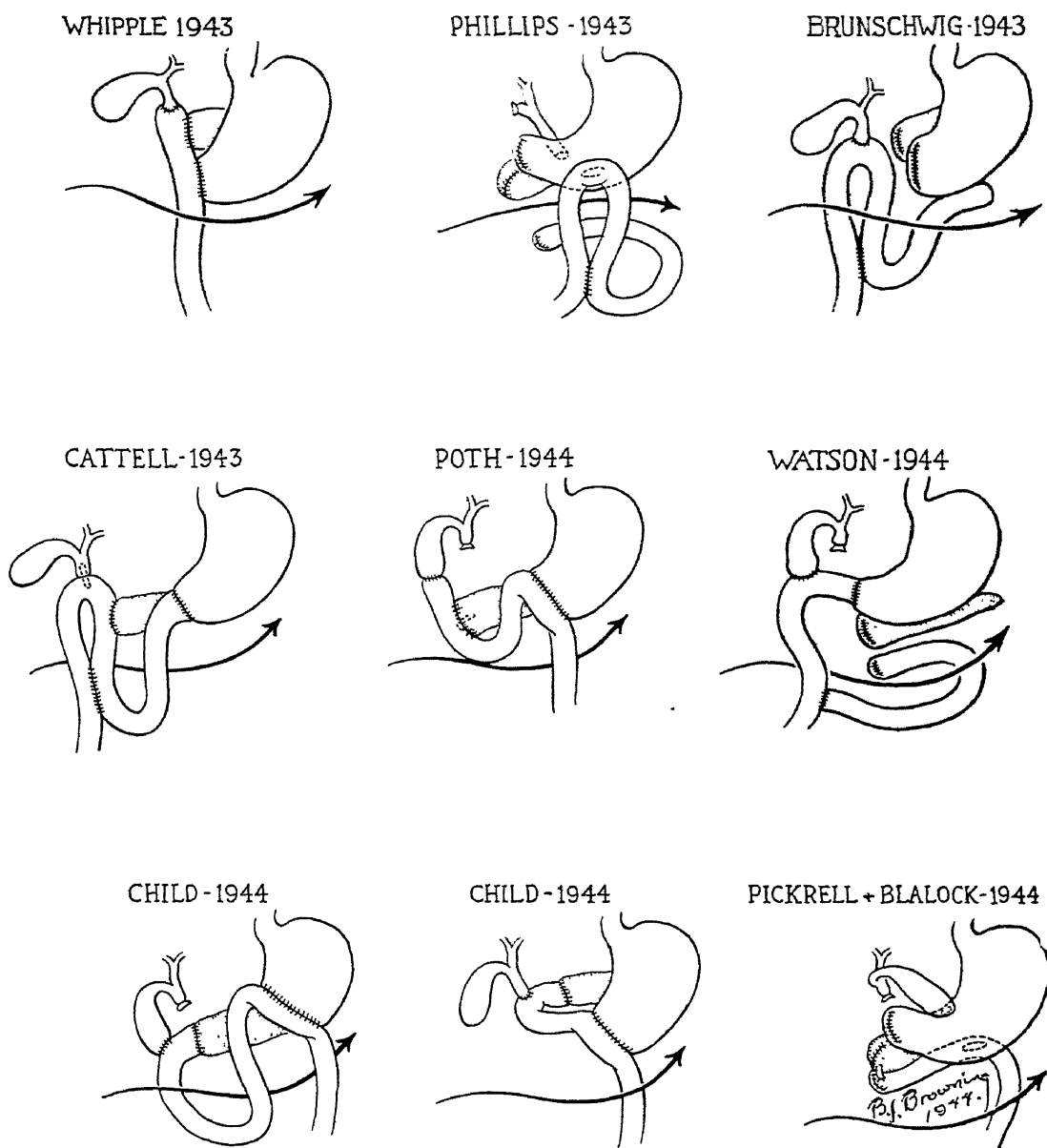


Fig. 5—Sketches illustrating various technics of pancreaticoduodenectomy continued: Whipple, Phillips, Brunschwig, Cattell, Poth, Watson, Child, and Pickrell and Blalock. (Orr, T. G.: Surgery 18: 154 (Aug.) 1945.)

pancreaticoduodenectomy. In three of the cases where a two-stage procedure was planned, two died following the first stage and one died on the operating table at the beginning of the second stage. These were the only immediate

mortalities. At the time of the report, the survival rate following operation varied from thirty-three months to twenty-one days. Four of the cases had a clinical diagnosis of carcinoma of the pancreas without operative procedure

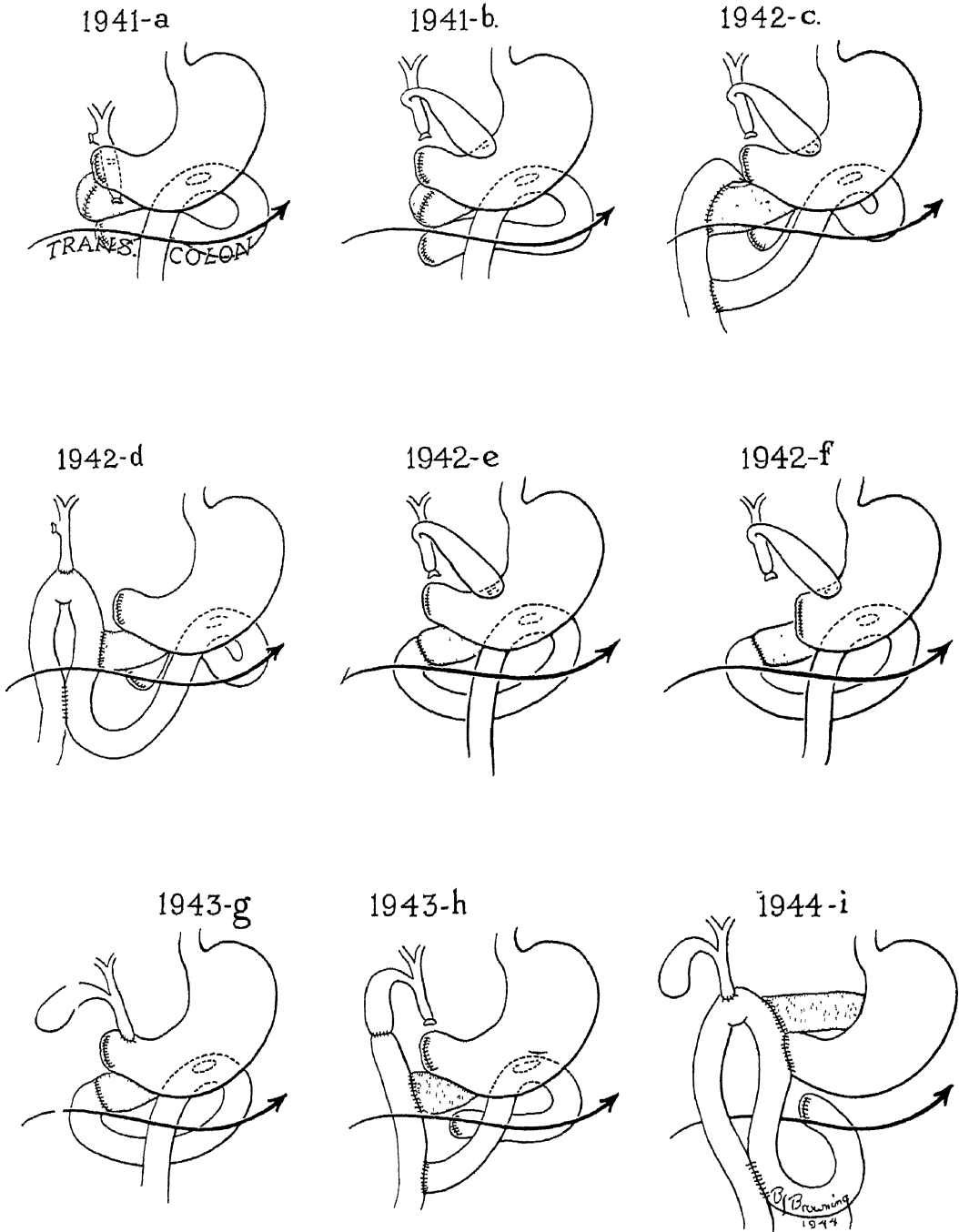


Fig. 6—Various techniques of pancreaticoduodenectomy used in nine cases in the University of Kansas hospitals. (Orr, T. G.: *Surgery* 18:154 (Aug.) 1945.)

and one case, dying of advanced pulmonary tuberculosis, showed a carcinoma of the head of the pancreas at autopsy. These were included in the series of eighteen cases.

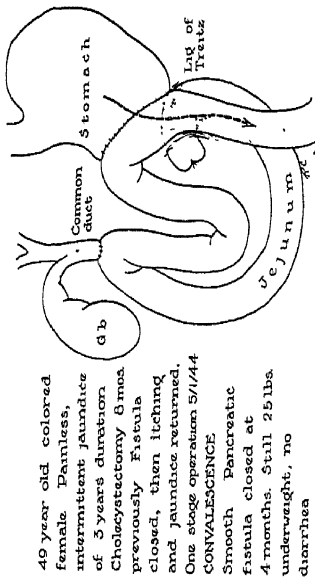
Orr<sup>18</sup> reported one of these cases in detail since a diagnosis of primary carcinoma of the duodenum was made. This patient was successfully treated by a one-stage modified Whipple operation, but died of metastases seventeen and one-half months following operation. Due to the few cases of primary carcinoma of the duodenum reported, the results of radical excision cannot be evaluated at the present time.

Cole and Reynolds<sup>19</sup> describe a new type of operation for resection of the duodenum and head of the pancreas for carcinoma. A long loop end-to-side anastomosis is made between the stomach and the jejunum, distal to the cholecystojejunostomy. This secures drainage of the biliary tract, proximal to the gastric anastomosis, and so avoids the danger attendant upon passage of food over the common duct opening. The chief advantage of this technic lies in the diminished operating time required and a reduction of the suture lines and anastomoses to a minimum. The jejunum is anastomosed to the cut end of the stomach with the distal end to the greater curvature, so that food passes downward by gravity into the jejunum instead of upward into the jejunum as it must in many operations previously recommended. The chief purpose of a long loop proximal to the end-to-side jejunostomy is to allow transplantation of the common duct, and the stump of the pancreas, into the jejunum proximal to the gastric anastomosis. They felt that transplantation of the stump of the pancreas into the intestines would be much more common in the future than it has in the past.

The historical background and various procedures used by different authors were reviewed. (See Fig. 7.) This illustration summarizes five cases of pancreaticoduodenectomy illustrating the type of operation performed upon each patient. The method of choice and the one described by the authors is illustrated under Case I. It is stated that an additional case using the technic illustrated under Case I has since been performed, but insufficient time has passed to determine the ultimate results.

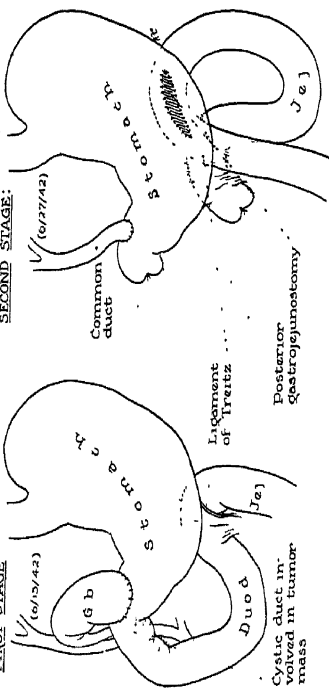
The transection of the duodenum proximal to the ligament of Treitz with inversion of the stump is considered an adequate and justifiable procedure unless the tumor extends to the ligament of Treitz. This eliminates the time consumed in dissecting the bowel from the mesenteric vessels. It also shortens the operative time. Anastomosis of the stomach to the loop of jejunum requires much less work than closure of the stomach and the performance of a gastroenterostomy. It does not seem to make much difference whether the jejunum is placed in an anterior or posterior colic position. The anterior colic type of anastomosis consumes less time since it is not necessary to close the defect in the mesocolon. Despite the variation of opinion in the literature concerning transplantation of the pancreas into the intestinal tract, the authors felt that this procedure was justifiable and would in the future become more common. It is also desirable to connect the jejunum in such a way that food will not flow over the site of transplantation of the common duct into the jejunum. This will minimize the possibility of an infectious cholangitis and also divert the food stream from the common duct, which has no valve to prevent its entrance into the biliary tract. This type of anastomosis also allows the food to pass from the

CASE I  
Carcinoma of the Ampulla of Vater



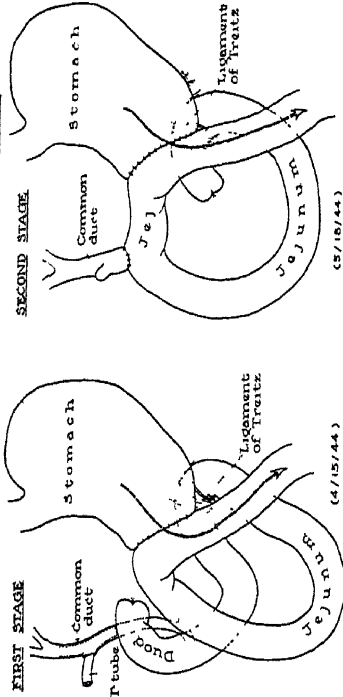
49 year old colored female. Painless, intermittent jaundice of 3 years duration. Cholecystectomy 8 mos previously. Fistula closed, then itching and jaundice returned. One stage operation 5/1/44 CONVALESCENCE Smooth Pancreatic fistula closed at 4 months. Still 25 lbs. underweight, no diarrhea

CASE III  
Cancer of the Head of the Pancreas



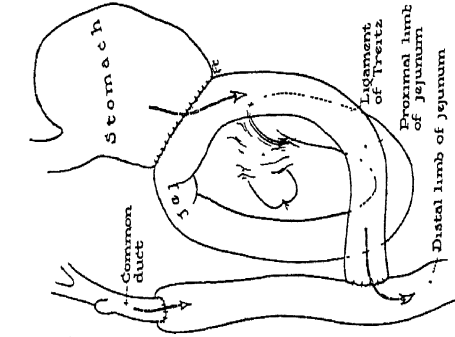
69 year old white male. Abdominal pain for 2 months. X-ray Stomach deformity Jaundice 10 days prior to entry Cholecystogastrostomy failure because cystic duct penetrated tumor in pancreas CONVALESCENCE Death on 9th postoperative day following 2nd stage. Autopsy: peritonitis.

CASE II  
Carcinoma of the Head of the Pancreas



59 year old white male. Abdominal pain, chills and fever began 3 weeks before his entrance Cholecystectomy imperative because of cholestasis. Therefore 2 stage operation necessary CONVALESCENCE Slow Pancreatic fistula still open after 7 months Nutritional disturbance. Protein loss with ankle edema, diarrhea Weight loss. Albumin 3.3, Globulin 2.2 Marked improvement on high protein diet

CASE IV  
Cancer of the Head of the Pancreas



54 year old white male. Weight loss of 25 pounds in last 2 months Jaundice and itching 1 month One stage operation 9/8/40 CONVALESCENCE Sign 9/8/40 Smooth, steatorrhea. Biliary drainage for 3 weeks Uroepsia. Intestinal obstruction at 9 months No metastases found at operation Complete recovery, now at work

CASE V

58 year old white male. Weakness and weight loss of 45 pounds in 15 months Cholecystectomy followed by chills and fever Improvement with a tube in cholecystostomy, drank bile daily Gained 12 pounds One stage operation 7/12/44 CONVALESCENCE: Rapid Paroxysmal auricular tachycardia 48 hours postoperative by Horri. 2 on 9th postoperative day Dietary difficulty Ankle edema, diarrhea, low blood proteins Improved on high protein diet

Fig. 7—Summary of our own five cases of pancreaticoduodenectomy, illustrating the types of operation in each patient. The method illustrated in Case I is the one preferred by us. (Cole, W. H. and Reynolds, J. T.: Surgery 18: 139 (Aug) 1945.)

stomach by gravity into the jejunum rather than forcing it upward from the stomach and thence downward into the jejunum. Detailed histories, operative findings, and pathological findings are reported for the five cases in which there was one mortality.

Strode<sup>20</sup> reviewed the known physiological properties of the pancreas as related to radical duodenopancreatic resection. He presented a case of carcinomatous degeneration of a duodenal diverticulum involving the head of the pancreas, in which successful radical duodenopancreatic resection was done. This was thought to be the first successful operation for this condition reported in the literature.

The patient was a forty-four-year-old Chinese male suffering from upper abdominal pain, discomfort, and diarrhea of five months' duration. There were six to eight stools daily, some of them were noted to have contained droplets of oil. There was a 15-pound weight loss, physical examination negative except for moderate tenderness in the upper abdomen; intermittent glycosuria with a normal glucose tolerance test; diminished amylase in the feces, and x-ray evidence of a space-taking lesion in the region of the head of the pancreas.

At operation three months later, the distal two fifths of the stomach, the distal one third of the common duct, the entire duodenum, the head and body of the pancreas containing the tumor were removed. The distal end of the severed jejunum was brought up behind the colon and fitted over the end of the pancreas, suturing the mucosa of the jejunum to the side of the pancreas with two continuous rows of A traumatic chromic catgut and one row of interrupted silk. The other anastomoses were completed by the same technique. The gallbladder was filled with stones; this was removed. Two small

stones were found in the common duct and these were removed. The duct was anastomosed to the jejunum over the proximal flared end of a short segment of a No. 16 rubber catheter. Beyond this, the stomach was anastomosed end-to-side to the jejunum, three soft rubber tissue drains were inserted—one in the region of the common duct anastomosis, and the others in the region of the pancreatic anastomosis. The incision was closed. On the eighth postoperative day, bile drained from the wound for about four days and then spontaneously ceased. (See Fig. 8.) The pathological diagnosis was a large ulcerated diverticulum of the duodenum with secondary adenocarcinoma involving the pancreas.

Observations on eighteen patients subjected to pancreatoduodenal resection were reported by Cattell.<sup>21</sup> Three deaths occurred. A one-stage operation was employed in five cases with one death, and a two-stage in twelve with two deaths. Many of these patients were over sixty years of age suffering with severe obstructive jaundice and poor general physical condition, which was thought to necessitate a two-stage procedure. A long loop, anticollic, cholecystojejunostomy was recommended since it permits rehabilitation and does not complicate the resection. Elevation of the pancreas and duodenum to determine operability should be done before dividing the stomach. Restoration of the external pancreatic juice in the intestines is accomplished by a direct anastomosis of the duct of Wirsung to the jejunum as a means of avoiding the serious complications accompanying pancreatic fistulas and in order that normal pancreatic and digestive functions may be accomplished. Anticollic gastric, biliary, and pancreatic anastomoses were advised. Results for a period up to two years were reported

with satisfactory results in thirteen of the eighteen cases.

Martiarena<sup>22</sup> describes a case of a tumor of the ampulla of Vater in a man forty-three, who suffered from attacks of alimentary intoxication of eight years' duration. He came for treatment following a severe attack of itching, icterus,

with chromic catgut was done. The patient improved under the administration of hypertonic *glucose* solution, *blood transfusion*, injections of *vitamin K*. As a substitute for pancreatic secretion, he was given *takadiastase* and *peptopancreas*. A pancreatic fistula drained for twenty-seven days and com-

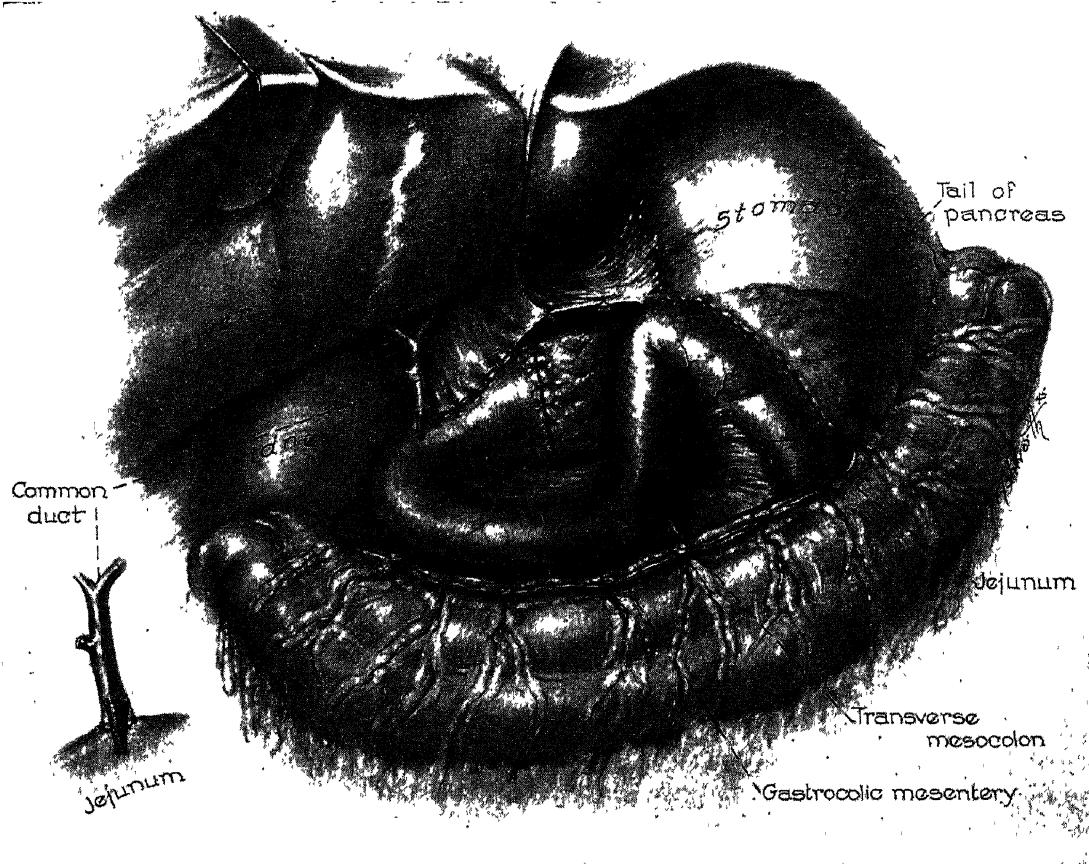


Fig. 8—Showing the anastomosis of the pancreas, common duct, and stomach to the jejunum. (Strode, J. E.: *Surgery* 18:122 (July) 1945.)

and acholia, at which time there was a probable swelling in the right hypochondrium. Operation revealed a lobulated tumor of the head of the pancreas, extending back to the mesenteric vessels and connected externally with the wall of the second part of the duodenum. Removal of the tumor after ligation of the vessels, and duodenopancreatectomy with suture of the stump of the pancreas

pletely closed forty days after the operation. Histological examination revealed an adenocarcinoma grade III of the ampulla, adenocarcinoma of the pancreas, and metastatic adenocarcinoma of the regional gland.

It was reported that of the 126 operations of this kind, 103 were performed before 1935, with a mortality of 33 per cent. Twenty-three were performed since

with a mortality of 15 per cent. Twenty-two of the patients survived three years or more. When the tumor is of the ulcerative type, it often invades the inner wall of the duodenum and the head of the pancreas and necessitates duodenopancreatectomy.

Erb<sup>23</sup> reports the case of a fifty-two-year-old female suffering from vague indigestion and gas pains of one year's duration, with a nonfunctioning gallbladder and a small extrinsic pressure defect on the duodenal cap who was thought to have an early malignancy of the pancreas or common duct. At operation, a greatly distended gallbladder and common duct were exposed. A movable mass was felt in the head of the pancreas and the gallbladder was drained and a radical resection of the duodenum and head of the pancreas was performed. The stomach was divided proximal to the pylorus and closed. The duodenum was liberated and divided 5 cm. distal to the lesion. The common duct was isolated, ligated, and divided, the closure being reinforced by interrupted sutures of silk. The body of the pancreas was bisected 3 cm. from the lesion. Two distinct ducts were separately ligated to the pancreas turned in with silk. The head of the pancreas was markedly adherent to the portal vein and had to be liberated by sharp dissection. The jejunum could not be brought in contact with the gallbladder without undue tension, so the gallbladder was anastomosed to the duodenum. Following this, a routine retrocolic posterior gastrojejunostomy was done. All anastomoses were performed with catgut for the mucosal suture and the serosal layers with silk. The postoperative course was smooth. On the third day there was profuse drainage from the stab wound which was assumed to be pancreatic juice. This ceased on the twelfth postoperative day. She was

discharged on the twenty-third postoperative day.

It was thought that radical resection of the head of the pancreas will result in permanent cure rarely, due to the intimate relationship of the pancreas to vital structures (portal vein), which cannot be sacrificed in a wide resection. However, life expectancy may be increased by this procedure.

**Body and Tail**—Brunschwig<sup>24</sup> points out that cancer of the body of the pancreas is discovered clinically late in the course of the disease and, while radical resection may be feasible, few patients are subjected to operation early enough in the evolution of these growths. He reports six instances of resection of the body of the pancreas with splenectomy and two instances of total pancreatectomy, with total duodenectomy, and splenectomy. The immediate operative mortality was 50 per cent (four cases, including the two total pancreatectomies). One patient with an islet cell carcinoma invading the entire body and later manifesting hepatic metastases lived three years and eleven months. Of the remaining three, two survived five weeks and five and one-half weeks respectively, despite metastases at the time of operation. Both experienced amelioration of the severe abdominal pain. The third is living, comfortable, and in fair general condition three months following resection of the body for carcinoma and subtotal gastrectomy for metastases to the stomach. Metastases to the falciform ligament and umbilicus were also resected. These cases are reported in some detail.

The steps in the technic are summarized as follows:

Anesthesia — Preferably continuous spinal.

1. High midline, transverse or inverted T incision.

TABLE II  
RESECTIONS OF THE BODY OF THE PANCREAS AND SPLEEN

<i>Case No.</i>	<i>Pathologic Condition</i>	<i>Course</i>
Case 1	Islet-cell carcinoma invading entire body.	Lived three years, eleven months. Died after third celiotomy as a result of portal vein ligation.
Case 2	Carcinoma, proximal portion of body. Few hepatic metastases.	Died third day (portal thrombosis?).
Case 3	Carcinoma invading entire body. Multiple hepatic metastases.	Lived five weeks. Died of carcinoma-tosis.
Case 4	Carcinoma of proximal portion of body and neck.	Lived nine days. Died of bile peritonitis. Portal vein ligated.
Case 5	Carcinoma arising in upper border of body.	Lived five and one-half weeks. Died of "exhaustion." Necropsy revealed single intrahepatic metastasis.
Case 6	Carcinoma of tail of pancreas, with metastasis to stomach and retroperitoneal lymph nodes.	Living three months after resection of body of pancreas and radical gastrectomy. Evidence of recurrence.

TOTAL PANCREATECTOMY AND DUODENECTOMY WITH SPLENECTOMY

Case 7	Entire pancreas replaced by carcinoma. Metastases in liver.	Died third day. Massive bilateral lobar pneumonia.
Case 8	Entire pancreas replaced by carcinoma. Metastases in liver.	Died ninth day of "exhaustion."

Immediate operative mortality, 50 per cent (four cases).

Survivals, four cases: 5 weeks; 5.5 weeks; 3 years, 11 months; one living 3 months in fair condition, respectively.

(Brunschwig, A.: Ann. Surg. 120: 413 (Sept.) 1944.)

2. Approach to the pancreas by transection of the gastrocolic omentum from the level of the head of the pancreas to the gastrosplenic vessels.
3. Retraction of the stomach upward and the transverse colon downward.
4. At this point, the body of the pancreas may be excised in one of three ways, depending upon the expediency of each situation:

(a) Transection of pancreas at the level of the neck with resection proceeding distally of body and tail; hemostasis being secured by ligation of branches from the splenic vessels.

(b) Division and ligation of gastrosplenic vessels, then transection of the neck of the pancreas and splenic artery and vein at this

level, with excision of body of pancreas and spleen *en masse* proceeding from the neck distally.

- (c) Division and ligation of gastrosplenic vessels, then elevation of spleen by grasping in the right hand; this brings the tail and body of pancreas forward together with splenic artery and vein. Transection of neck of pancreas and splenic vessels at level of superior mesenteric vessels with excision of body of pancreas and spleen *en masse*.
5. Interrupted interlocking silk mattress sutures are placed about 0.5 cm. proximal to the cut edge of the remaining neck of pancreas. The transected main pancreatic duct, if apparent, is grasped with a hemostat and ligated separately.



- 6 The transverse mesocolon is repaired except in the region below the pylorus. Here, one or two soft-rubber drains are inserted to the site of pancreatic transection.
7. Closure of the abdominal wound.

In some instances of redundant stomach, the gastrohepatic omentum may be transected, the stomach retracted downward and the body of the pancreas excised over the lesser curvature of the stomach.

6. The pylorus was transected several centimeters proximal to the pyloric sphincter and upper segment of stomach closed.

7. The common bile duct was transected below the level of the superior border of the first portion of duodenum.

8. The head of the pancreas and duodenum were completely mobilized and lifted away from the superior mesenteric vessels, the uncinate process of the pancreas and terminal portions of duodenum brought out to the right from beneath these vessels after transection of ligament of Treitz.

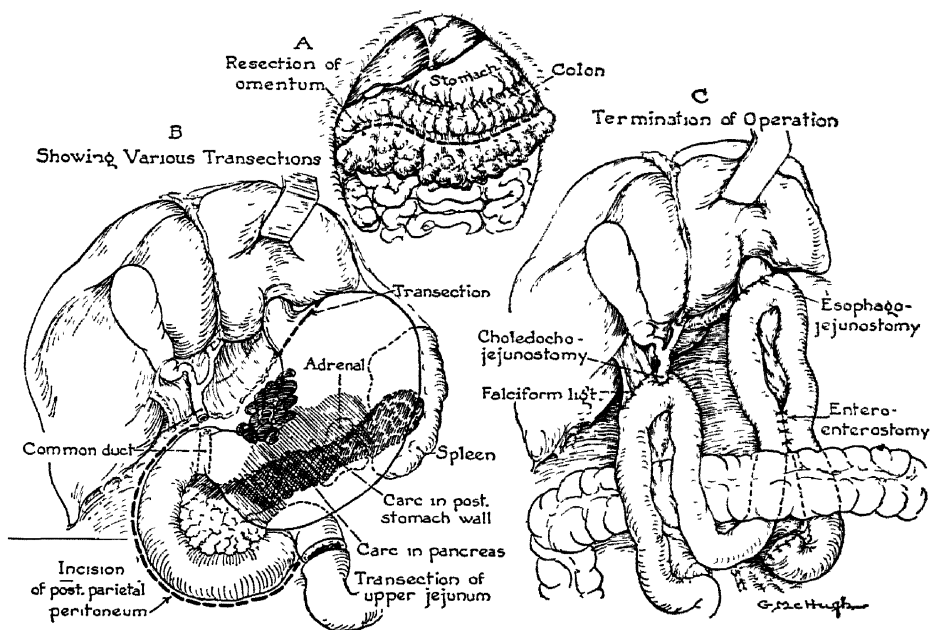


Fig. 9—Various steps in operative procedure. (Brunschwig, A., et al.: Surg., Gynec. & Obst. 80: 253 (March) 1945.)

Total duodenopancreatectomy and splenectomy for practically complete replacement of the pancreas by carcinoma was performed in two patients as follows:

1. In each instance, the pancreas was exposed via the gastrocolic route.
2. The gastrosplenic vessels were divided.
3. The spleen was grasped with the right hand and elevated to mobilize the body of the pancreas.
4. The splenic vessels were divided about 3 cm. distal to the origin of the portal vein.
5. The peritoneum along the convex border of the duodenum was incised to mobilize the head of the pancreas and duodenum.

9. Transection of jejunum just distal to ligament of Treitz and closure of distal segment.

10. Removal of entire pancreas and duodenum with attached lower pylorus and spleen.

11. Gastroenterostomy (Billroth II).

12. Cholechojejunostomy, using loop of jejunum about 15 cm. distal to above anastomosis; jejunojejunostomy between loops of cholechojejunostomy.

### Total Pancreatectomy, etc.

A male, aged fifty-three, complaining of watery foamy stools of two years' duration with a loss of 50 pounds, who recovered following a total pancreatec-

tomy, gastrectomy, duodenectomy, splenectomy, left adrenalectomy, and omentectomy was reported by Brunschwig *et al.*<sup>25</sup> The steatorrhea was confirmed and the patient was found to be a severe diabetic. X-rays of the stomach, duodenum, chest, and colon were negative. After a period of six months' improvement on medical treatment, the patient was readmitted due to severe pruritus, icterus, and pain in the right upper quadrant. At operation, carcinoma of the body of the pancreas, with invasion of adjacent viscera, was found. The diabetes was not aggravated following the operation—there were periods when the diabetes seemed to be less severe than before operation. The insulin requirements were 30 units of protamine zinc and 10 units of regular insulin daily on a carbohydrate equivalent of 400 gm.

It was felt that this experience demonstrated the feasibility of very radical resection for abdominal carcinoma. The patient remained in fair condition and ambulatory for approximately two and one-half months. At the end of three and one-half months, death occurred and an autopsy revealed abdominal carcinomatosis.

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## THE GASTROINTESTINAL TRACT

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### Management of Gastric Resections

The selection of any patient for gastric resection requires on the part of the surgeon not only careful information as to the precise reasons for gastric resection, but also a consideration of the patient's age, nutrition, cardiovascular status, anemia, and protein reserves. Old

age is no absolute contraindication to gastric resection. The state of the patient's nutrition and the degree of anemia, however, are of great importance. The patient's cardiovascular status is also very important. Patients who have had coronary infarcts, chronic asthma, or bronchitis make very poor operative risks.

**Preoperative Care**—The preoperative preparation of the patient for gastric surgery may require several days or even weeks and demands particular attention to details. Particular attention is paid to the correction of anemia and hypoproteinemia. One or more blood transfusions are given preoperatively. Plasma transfusions and intravenous amino acids are given to restore the protein stores. In anticipation of possible multiple transfusions, Rh factor determinations are done preoperatively. On the more debilitated patients with low serum protein, Clute and Howe<sup>1</sup> have performed preliminary jejunostomies for preoperative and postoperative jejunal feedings. A careful dietary history and blood cevitic acid levels preoperatively give useful information regarding the vitamin C needs. This is administered in the form of 100 mg. cevitic acid tablets three times a day by mouth if there is no obstruction. If there is obstruction, 500 mg. daily are given intravenously. Vitamin B is given in maximum doses also. Prothrombin time values are also performed and vitamin K is administered when indicated. Electrocardiographic tracings and cardiac consultation are obtained to serve as a base line and aid to the consultant later, in the event of possible pulmonary or cardiac complications. Occasionally, the differential diagnosis between coronary disease and pulmonary embolus is a difficult one and a preliminary electrocardiographic tracing is a welcome aid. A routine preoperative chest film is taken, not only to rule out metastasis in cancer cases, but also to serve as a comparison film later in the event of pulmonary complications. Although nonprotein nitrogen determinations are routinely carried out, a carefully done phenolsulfonphthalein excretion test is a much finer index of early renal damage and serves as a warning to greater

care in fluid and electrolyte balance consideration. In cases with pyloric obstruction, a Levine tube is passed with Wangenstein suction for some days. Lavage with 0.5 per cent hydrochloric acid in normal saline solution should be done 12 hours before the operation, and continued until the washings return clear.

All patients for gastric resection come to the operating room with a Levine tube in the stomach with suction.

**Operative Procedure**—Spinal anesthesia is preferred. Continuous spinal anesthesia, following the technic of Lemon has advantages for prolonged procedures. Occasionally, the patient must be given pentothal intravenously or some gas-oxygen anesthesia to abolish traction reflexes and to avoid general discomfort.

**Postoperative Care**—The Levine tube is attached to Wangenstein suction. Careful precautions are taken to prevent atelectasis. Twelve hours after operation, the patient's position in bed is changed hourly from side to side. Deep breathing is encouraged. If it is evident that there are excessive secretions collecting in the bronchi and trachea, the patient is given inhalations of carbon-dioxide oxygen with a bedside tank and mask. When atelectasis is present, the secretions are removed by direct bronchoscopy.

A Levine tube left in place for any length of time is a hazard and predisposes to upper respiratory infection.

As a supportive measure to insure adequate oxygenation of the blood, oxygen is given by means of a nasal catheter or a B. L. B. mask. The patients are given water by mouth on the first postoperative day, 0.06 cc. every one-half hour. On the following day, this is increased to 0.12 cc. every one-half hour, and by the third day they are taking 60 cc. an hour. Malted milk is taken

on the fourth and fifth days, gruels, jello, and custards on the sixth, and fluids as desired with soft boiled eggs and cooked cereals by the seventh day.

Supplementary vitamins are administered in the intravenous fluids and intramuscularly until the patients can tolerate them by mouth.

A frequent check of the red cell count, blood chloride, cevitic acid, and total protein levels serves as a guide in the administration of intravenous fluids, whole blood, plasma, and amino acids.

### Chronic Peptic Ulcer of the Duodenum

In what may be termed a continuing study of 260 patients who were operated upon for peptic ulcer of the duodenum of from four to twenty years' duration by Rienhoff,<sup>2</sup> the results indicate that only 204 patients, or 78 per cent, should be regarded as well; 30 patients, or 12 per cent, as improved, and 21, or 8 per cent, as unimproved. The immediate mortality was 2 per cent with no deaths occurring in the last 160 cases. These patients were operated upon because of complications arising from a chronic peptic duodenal ulcer that would not respond to medical treatment. The complications consisted of intractable pain, hemorrhage, and vomiting associated with pyloric obstruction.

A conservative resection of the stomach and first portion of the duodenum was performed because resection, while far from ideal, was thought more efficacious than less radical procedures, such as gastroenterostomy. The surgical procedure has been: (1) To remove the pylorus, pyloric antrum, and a portion of the acid-secreting mucosa of the fundus; (2) to shunt the flow of acid chyme and food away from the ulcer-bearing area of the duodenum, and (3) to employ a type of anastomosis which

insures the maximum irrigation of the remaining pouch of stomach and at the same time prevent pooling of gastric juice and food due to delayed emptying. The rationale of the operative procedure, an antecolic gastrojejunostomy, is based upon the following considerations: (1) If the flow of gastric contents can be diverted from the duodenum, chronic peptic ulcers of this structure will heal or will fail to recur when excised. In over 75 per cent of the patients of this series, the ulcers were left *in situ* and apparently healed; (2) the operation must protect the patient from the development of postoperative complications in the jejunum, such as peptic jejunal ulcers or hemorrhagic jejunitis; (3) the original operation must have been so performed that in the event of jejunal complications, secondary operations may be carried out with minimal technical difficulty and operative mortality.

Extensive and hazardous dissections of ulcers located in the lower portion of the duodenum are unnecessary. If the ulcer is on the posterior wall and has produced massive hemorrhage and the patient is in shock, the better procedure is simple transfixion or cauterization, or both, of the bleeding vessel in the base of the ulcer.

In this series, division across the fundus of the stomach was made at right angles to the curvatures, greater and lesser, at the level where the left gastric vessels leave the lesser curvature and spread over the anterior and posterior surfaces of the stomach. This procedure insures removal of roughly 50 per cent of the organ, including the pylorus, the pyloric antrum, and about one third of the acid-secreting area. The removal of the antral mucosa is felt to be important because of the elimination of the hormone gastrin, the chemical stimulant for the formation of gastric juice. Also

removed is an indefinite amount of acid-secreting mucosa.

The results in this series seem to indicate that conservative resection of the stomach may be carried out with an immediate mortality as low as that following gastroenterostomy. Therefore, this type of resection is to be preferred to gastroenterostomy in the kind of case under discussion. The remote results also indicate that resection, regardless of the extent short of almost total gastrectomy, will not insure against the development of jejunal complications. The success or failure of a resection of the stomach for peptic ulcers of the duodenum depends, therefore, in the majority of patients, upon a permanent reduction in gastric acidity under the normal circumstances of the patient's everyday life. This reduction is accomplished in three ways: (1) By removal of the acid-stimulating hormone gastrin; (2) by reduction of the acid-bearing area by partial removal, and (3) by neutralization of the acid juice by a thorough mixing with the alkaline jejunal contents.

**The Treatment of Perforated Duodenal Ulcers**—Graham and Tovee<sup>3</sup> discuss the management of 114 patients with perforated duodenal ulcers. All but three of the patients were submitted to operation. There were ten deaths. All three patients not operated upon died. Of these three, one patient refused operation. The second patient refused and later consented, but died in the operating room before surgery could be undertaken. A diagnosis was not made in the third patient until the autopsy was performed. This showed a perforation of the duodenum which had localized as a left subphrenic abscess with the terminal factor being a rupture into the bronchus. The patient drowned in his own pus.

There were seven operative deaths in 111 operations, a mortality of 6.3 per cent. There were forty-nine consecutive operations without a death. The fiftieth patient died of a pulmonary embolus on the twelfth day after operation. The second and third patients died of pneumonia. The fourth patient developed uremia and died from this cause. The fifth patient died from an unrecognized pelvic abscess which ruptured into the general peritoneal cavity. The sixth patient died from a subphrenic abscess which was unrecognized postoperatively until it ruptured into the bronchus. The seventh patient, a senile man who could not be kept in bed, developed pneumonia and died from this cause three weeks postoperatively.

The age of the patients varied from sixteen to eighty-three years. There were as many deaths in patients under fifty as over fifty years of age. The interval between the onset of symptoms and the operation had been quite short in most instances. Bacteriological studies of the peritoneal exudate in fifty-nine patients showed no growth in thirty-four. Of the twenty-five which showed organisms in culture, there was one instance of pure culture of typhoid bacilli in a patient who twenty years ago had suffered from typhoid fever. There were only two instances in which colon bacilli grew on culture. There was only one case in which there was a growth of hemolytic streptococci. This occurred in a forty-nine-year-old man with a twelve-hour perforation, who had a perfectly uneventful convalescence and whose peritoneal cavity was closed without a drain. The other instances in which a positive culture was found included nonpathogenic organisms as nonhemolytic streptococcus, *Streptococcus viridans*, diphtheroid bacilli, and *Staphylococcus albus*, the latter probably being a contamina-

tion. The authors have been impressed with the soundness of the conception that the nutritional disturbance of the patient at the time of the perforation is a very important factor in contributing to the seriousness of his emergency. Their experience has led them to believe more firmly in correcting the patient's

enters the operating room with a Levine tube in the stomach and an intravenous infusion of glucose and saline solution already running. Sodium pentothal as a supplement to spinal anesthesia is used to overcome any apprehension or restlessness on the part of the patient. Three interrupted catgut sutures are placed

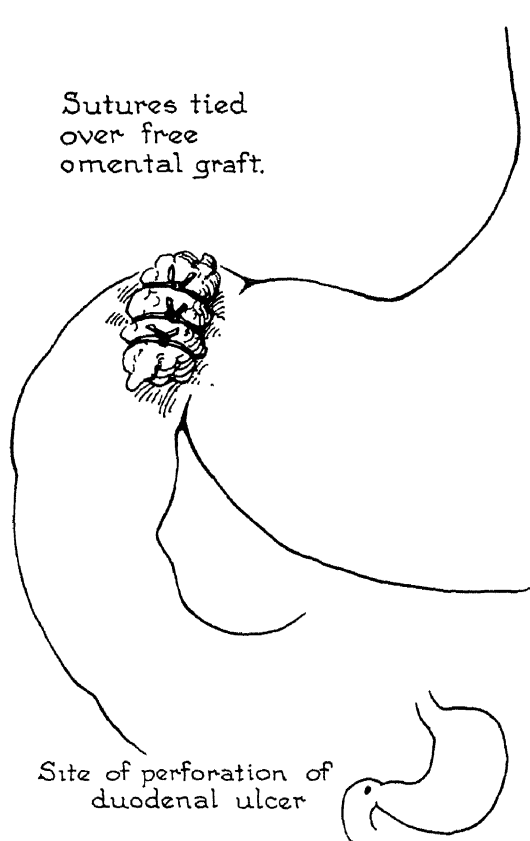


Fig. 1.

Fig. 1—The placing of sutures in relation to perforation. (Graham, R. R. and Tovie, E. B.: *Surgery* 17: 710 (May) 1945.)

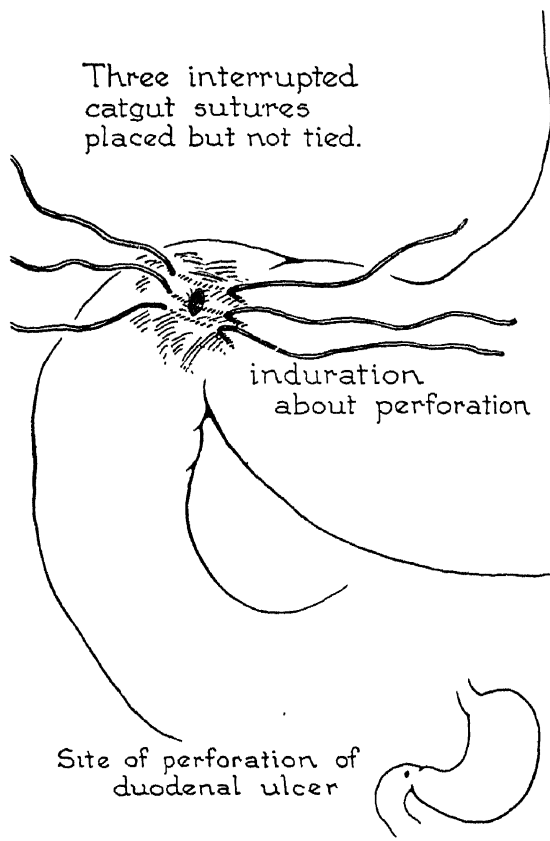


Fig. 2.

Fig. 2—Sutures tied over free omental graft. No attempt is made to close the perforation by the sutures. They are tied only sufficiently tight to hold the grafts *in situ*. (Graham, R. R. and Tovie, E. B.: *Surgery* 17: 710 (May) 1945.)

nutritional disturbance and biochemical imbalance before operation is undertaken. They are firmly convinced that the use of a spinal anesthetic is ideal. They use local block anesthesia in the abdominal wall, plus splanchnic block anesthesia transperitoneally in the patients who are too ill for spinal anesthesia. The patient

parallel to the long axis of the duodenum, one above, one below, and one across the perforation.

The authors then lay over the perforation a piece of omentum, either attached or detached, and then tie the sutures just sufficiently tight to hold the omental patch in position. The su-

tures are not tied tight enough for an attempt to be made to close the perforation. They simply hold the omentum over the perforation so that fibrin forms in this area. If there is gross soiling of the peritoneal cavity, the exudate is sucked out, without traumatizing the intraperitoneal contents. The abdomen is closed without drainage. The authors have not used any of the sulfonamide drugs routinely in the peritoneal cavity.

On the patient's return to the ward, his condition is grave, he is placed in an oxygen tent and given sufficient sedative to control the pain. The intravenous administration of saline solution and glucose is maintained, and the stomach is kept empty by aspiration of the indwelling duodenal tube. The patient's position is changed every two hours and he is encouraged to exercise the legs. Overbreathing is stimulated by the administration of carbon dioxide every two to four hours for the first twelve hours postoperatively and he is encouraged to cough.

If the patient is not doing well, there are three areas which must be examined immediately: First, the chest; second, the subphrenic spaces, and third, rectal. There is one pitfall in the investigation of the subphrenic spaces. If the patient has been operated upon under spinal anesthesia, x-ray studies which show free gas under the diaphragm must not be taken as evidence in the support of a subphrenic lesion, since air will normally occupy the subphrenic space in patients who have had a laparotomy under spinal anesthesia for as long as six weeks following operation.

It is the belief of Black and Blackford<sup>4</sup> that the judicious choice of the method of anesthesia, the use of small incisions and the limitation of the operation to simple closure of the perforation, preferably by patching, should be fol-

lowed by the best immediate recovery rate. There is a definite trend toward spinal anesthesia.

The frequency of wound complications following operation for perforated peptic ulcer is well known. Wound infection occurred in twelve of the ninety-three cases in which operation was performed at the Mayo Clinic and evisceration occurred in one of the cases. Of the several methods which have been proposed to minimize the consequences of wound infection and poor healing, the use of nonabsorbable sutures, small vertical or transverse incisions, and secondary and delayed closure of wounds would seem to be the most important. The authors prefer a small incision (8 to 10 cm.) high in the right rectus muscle. The incision is closed with nonabsorbable interrupted sutures which include all of the layers of the abdominal wall. In addition to the retention sutures, which are placed approximately 1.5 cm. apart, the individual layers are sutured with surgical catgut. Patching with a piece of omentum was used more frequently than closure with sutures. If drainage of the stomach is necessary, an inlying tube with constant gravity suction may be employed.

Of the eleven hospital deaths in the series of ninety-three cases in which operation was performed, six were due to peritonitis, three were due to bronchopneumonia, and two to pulmonary embolism. Of the nonfatal complications, those pertaining to the abdominal wall were the most numerous. The wound became frankly infected in ten cases; in four of these cases, considerable separation of the wound occurred and in one case nonfatal evisceration developed. Localized intraperitoneal abscesses developed in three cases and pulmonary complications, such as pulmonary embolism, atelectasis, and bronchopneumonia, were

observed in seven cases. Parotitis and thrombophlebitis each were observed in two cases. The three patients not operated upon died.

### **A Plan for the Surgical Management of Gastrojejunal Fistula**

Gastrojejunocolic fistula is a serious complication of peptic ulcer because the presence of such a communication between the stomach, jejunum, and colon so profoundly influences the nutrition and health of the individual affected and because the treatment involves such a complicated and hazardous surgical procedure. The cause of death in most cases has been peritonitis resulting from contamination during operation or from leakage from suture lines, or shock attending an extensive technical procedure. Pulmonary complications such as pneumonia, embolism, and occasionally hemorrhage, cardiac, or renal failure account for other postoperative fatalities. Marshall<sup>5</sup> discusses certain details of the problem of gastrojejunocolic fistula, outlines the operative procedure employed at present in the Lahey Clinic, and reports on fourteen cases in which this method was used. Gastrojejunocolic fistula most commonly occurs following operation for duodenal ulcer and in the majority of cases follows posterior gastroenterostomy. In his group of fourteen cases, twelve patients had had posterior gastroenterostomy, and two had had an insufficient gastric resection, the original operation in all instances being undertaken for duodenal ulcer. The majority of gastrocolic fistula follow operation for duodenal ulcer and result from jejunal or gastrojejunal ulceration at the site of gastrojejunal anastomosis. Recurrent marginal ulcer always precedes the development of the fistulous communication and may occur years after the initial operation. In one case in this

group the fistula developed twenty years after an insufficient gastric resection. In view of the high incidence of gastrojejunocolic fistula following posterior gastroenterostomy, it is evident that certain precautions are imperative to prevent this serious complication. Gastroenterostomy is a valuable operation, but has a limited application and should be employed only when subtotal resection is definitely contraindicated because of the age of the patient, because of poor physical condition, and in the presence of certain technical difficulties that would make gastric resection hazardous. Furthermore, if resection is undertaken for ulcer, a considerable portion of the stomach must be removed. The majority of the cases reported have occurred after posterior resection and posterior gastroenterostomy. It is important that when posterior gastroenterostomy is employed, the anastomosis should be made through an opening in the mesocolon placed near the base of the mesocolon and as far as possible from the colon. It is important to remember that evidence of increased colon irritability occurring in a patient with symptoms of recurrent ulcer indicates that the colon is adherent to the area of inflammation about the gastrojejunal anastomosis, and is evidence of impending perforation. Operation should be advised and carried out as early as possible to prevent the serious complication of gastrojejunocolic fistula.

The symptoms of gastrojejunocolic fistula are characteristic and in the majority of the cases the diagnosis can be readily established. Recurrent distress occurring after operation, either gastroenterostomy or resection for peptic ulcer, suggests gastrojejunal ulcer. The development of diarrhea with weight loss is strongly presumptive evidence of gastrojejunocolic fistula. Pain at first



may be severe and with perforation into the colon may subside, but in the majority of the cases it continues as epigastric distress. The history of belching of foul gas or vomiting of foul

hydration, nutritional edema, hypoproteinemia, anemia, and serious states of vitamin deficiencies are often encountered. Roentgenologic examination readily confirms the clinical diagnosis.

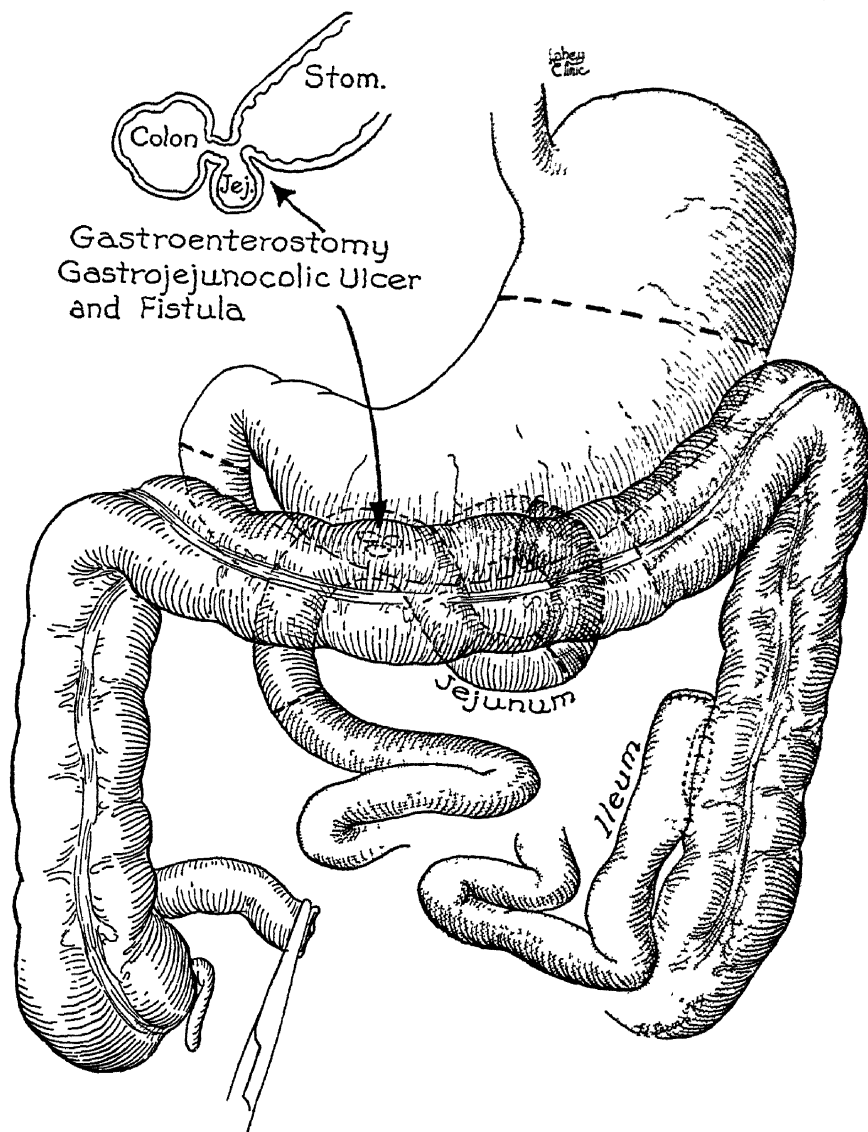


Fig. 3—First stage of operation for gastrojejunocolic fistula. The terminal ileum has been divided, the proximal end of ileum has been closed by inversion and a side-to-side anastomosis between the terminal ileum and descending colon has been established. The distal end of divided ileum is likewise closed by inversion and dropped back into the abdomen. The light segments indicate the portions of stomach, colon, and jejunum which are to be removed at the second operation. (Marshall, S. F.: *Ann. Surg.* 121: 620 (May) 1945.)

stomach contents may be obtained in many cases. The stools are watery, frequent, and often contain undigested food particles. Weight loss is often extreme. In addition to emaciation, de-

The treatment is purely surgical and the surgical management of a large gastrojejunocolic fistula is technically difficult and often accompanied by considerable operative risk. The generally poor

condition of these patients, the stage of malnutrition, the marked alteration in protein and blood chemistry findings make any extensive operative procedure, without measures to improve these states, entirely unsafe and, consequently, unwise. The operative plan consists of a two-stage procedure and employs the principle of block excision of the section

Small intestinal and right colon contents are thus emptied into the descending colon and cannot reenter the stomach and jejunum. The toxic and irritating efforts of such regurgitation are thus avoided and these patients have tended to improve in nutrition, gain in weight, and, in most instances, have cessation of diarrhea.

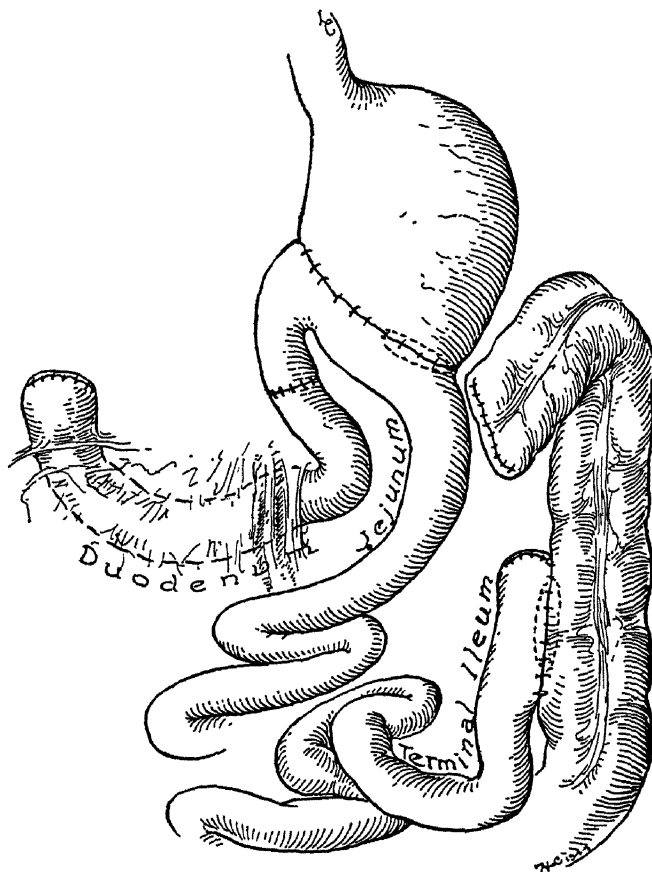


Fig. 4—Second stage of operation for gastrojejunocolic fistula. Drawing illustrates the completed operation. Note that the right colon and transverse colon to a point past the fistula, together, with the portion of the jejunum involved with ulcer, have been resected. A gastric resection completes the operation. (Marshall, S. F.: *Ann. Surg.* 121: 620 (May) 1945.)

of jejunum and colon involved, plus gastric resection. The first stage of the operation is designed to divert small intestinal and colonic contents from regurgitating into the stomach and jejunum. This is accomplished readily by dividing the terminal ileum and performing an ileocolostomy between the terminal ileum and descending colon.

When the method was first used, a second stage was carried out in about two weeks after the first stage. It became evident that a larger interval should elapse between stages in order that the patient's nutrition and general condition could improve. It is now an established practice to send these patients home for a period of two or three months before

completing the operation by the second-stage procedure. A diet high in vitamins, protein, and calories is given during this period.

In the second and final stage of the operation for gastrojejuno-colic fistula, the cecum, right colon, and transverse colon are mobilized to a point distal to the colonic fistula. All mesenteric attachments are divided. The transverse colon beyond the fistula is then divided with the actual cautery between clamps and the end of the distal portion of the transverse colon is inverted with catgut sutures, which are reinforced with interrupted silk sutures. The colon and attached stomach may then be turned forward and the involved loop of jejunum is readily visualized and likewise resected. A high resection of the stomach after mobilization and division of its attachment completes the block excision of the fistulous tract and involved viscera. An end-to-end jejunal anastomosis is carried out before completing the gastrojejunal anastomosis.

### Hemangioma of the Intestine

Hemangioma of the intestinal tract is rare and is frequently overlooked in differential diagnosis. In most cases, surgery at the proper time will effect a cure, while the mortality in those untreated is extremely high. Hemangiomas of the intestine vary tremendously in type, distribution, and course. Kaijser (1937) divides these angiomas into four groups as follows: (1) Multiple phlebectasia consists of dark bluish red nodules ranging in size from pinhead to pea, which are scattered over a limited portion of the intestine. These are usually in the submucosa though they may be subserous and are usually opposite the mesentery. Each one is connected with one of the smaller veins and is made up of communicating cavities.

These are probably not true tumors but may be the result of some back pressure, although they are often given as examples of hemangioma of the intestinal tract. There are usually no clinical symptoms. (2) Cavernous hemangioma is divided into those developing by diffuse permeation in the intestinal wall and into those growing more compacting, thus frequently becoming polypoid. These are the angiomas particularly prone to cause hemorrhage or obstruction. (3) Simple hemangioma or capillary hemangioma is a network of dilated capillaries as compared to the large blood-filled, thinly lined, communicating cavities of the cavernosa type. The simple type usually appears as a round submucous tumor, up to a plum in size, protruding into the canal and covered by normal mucosa. (4) Angiomatosis covers the occurrence of multiple angiomas varying in structure from the usual cavernous type to one rich in cells and stroma, some even suggesting angiosarcoma.

While many angiomas give no sign of their presence, others may show most alarming symptoms requiring immediate interference. The characteristic symptom is hemorrhage, often beginning in infancy. The bleeding may be undetected and yet be accompanied by a true anemia of long standing even associated with asthenia and cachexia. In other cases, hemorrhage is severe enough to cause death. Less frequent is obstruction which may be due to polypoid encroachment on the intestinal lumen, to an encircling mass with added edema or to intussusception. Acute obstruction seems more common than the chronic. A third symptom is due to acute inflammation of the tumor for which reason a diagnosis of appendicitis has been made in patients found to have instead angioma of the terminal ileum.

Diagnosis before operation is rare. There are no diagnostic signs of certainty except in those tumors visible by endoscopy. Barium x-ray may in some reveal an intestinal tumor but does not suggest its nature. Kaijser emphasizes repeatedly and noted in his own two cases the presence in the x-ray film of numerous rounded shadows of calcium density in the region later found to be the tumor site, these apparently being shadows of phleboliths within the angioma. This diagnostic sign he believes is usually confined to the cavernous type of hemangioma. In general, unexplained intestinal bleeding, in small or large amount, especially of long standing, is the most typical sign and requires at least consideration of hemangioma as a diagnosis.

The danger of intestinal hemangioma depends largely on its type. Multiple phlebectasia seldom gives signs. In simple hemangioma an occasional death from hemorrhage has been reported. The prognosis is much more grave in cavernous hemangioma. Some are too extensive for extirpation; in others, acute hemorrhage or obstruction makes operation imperative at an unfavorable stage or death may occur without operation.

Nearly all of the cases successfully treated have been surgical resections. Cauterization or partial extirpation usually has given only temporary relief. X-ray has given improvement in some cases though local radiation, as by the use of implanted radon seeds, is seldom the practical procedure that it is on body surfaces. The injection of a coagulating substance gave a brilliant result in Bancroft's (1931) case.

### **Primary Malignant Disease of the Small Intestine**

Primary malignancy of the small intestine is a challenge to modern surgery

because of its rarity, difficulty of early diagnosis, extensive technic required, high operative mortality and grave prognosis. For this reason a study was made by Shallow<sup>6</sup> of thirty-eight consecutive cases of histologically proven primary malignancy of the small bowel encountered in the Jefferson Medical College.

**Incidence**—Primary small intestinal malignancy occurs in 0.1 per cent of all general autopsies. Malignancy in general occurs with about equal frequency in each of the three divisions of the small intestine. Carcinoma is found twice as often as sarcoma and the ileum ranks lowest for carcinoma but highest for sarcoma. Of 305 collected primary duodenal carcinomas, Eger (1933) found 62 per cent in the second portion, 24 per cent in the first, 12 per cent in the third portion, and 2 per cent involved the entire duodenum. Small intestinal carcinoids comprise 0.02 per cent of autopsy and surgical specimens, 8.3 per cent of all small intestinal neoplasms and occur chiefly in the ileum but occasionally in the jejunum and duodenum.

**Pathology**—Primary carcinomas of the small intestine are divided by their gross morphology into three types, which, in order of frequency, are the stenosing, the infiltrating or ulcerative and the polypoid. Primary sarcoma usually extends toward the mesentery without producing obstruction (exception) or hemorrhage, in contradistinction to carcinoma. Carcinoids are usually small, firm, submucosal yellow nodules which rarely produce obstruction, grow slowly, and metastasize in 25 per cent chiefly to the regional nodes and only occasionally to the liver. Thirty-one of the thirty-eight cases of primary small intestinal malignancy in this series had evidence of extension or metastasis most frequently to the regional nodes and liver. Of the

seven duodenal carcinomas, there was no metastasis in one, regional node involvement in one, and widespread metastasis in five.

Parsons and Mullins (1935) believe that ampullary malignancies first extend along the common duct and into the

widespread metastasis. There were no malignant carcinoids.

**Diagnosis**—The early diagnosis of primary malignancy of the small intestine is dependent upon careful evaluation of the history, physical, laboratory, and roentgen ray findings. Among these

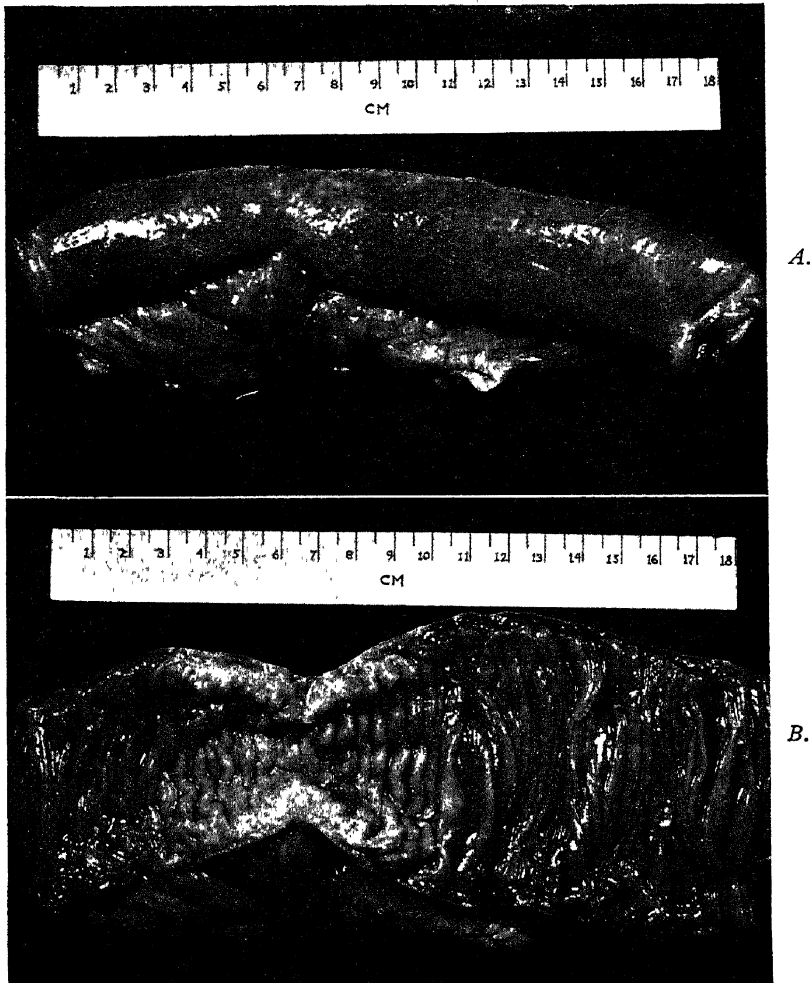


Fig. 5—*A*, Stenosing adenocarcinoma of the jejunum. *B*, Opened specimen of stenosing adenocarcinoma of the jejunum. (Shallow, T. A., *et al.*: *Am. J. Surg.* 69: 377 (Sept.) 1945.)

pancreas. In Shallow's group of seven ampullary lesions, all of which were carcinoma, five showed metastasis, but the pancreas was only involved in one. Of the twenty-four jejunal and ileal malignancies, four were without evidence of extension or metastasis, nine involved only the regional nodes, and eleven had

thirty-eight cases, the onset of symptoms was usually insidious, although occasionally it was sudden with a perforation, a severe hemorrhage, or an acute intestinal obstruction; the duration of symptoms varied from five days to three years, with an average of seven months. Lesions of the ampullary portion pro-

duced biliary obstruction before intestinal obstruction in all cases; occasional intermittency and variation in intensity of the jaundice may result from sloughing of the tumor, increased intrabiliary tension forcing bile through the point of constriction and the subsidence of papillary edema. Over 75 per cent of the small intestinal neoplasms in this series were palpable, usually fixed in the duodenum and mobile in the jejunum and ileum. Laboratory studies not only aided in the diagnosis, but also in determining

**Treatment and Results**—In addition to decompression of the gastrointestinal tract, it is essential that these patients be improved medically to a maximum degree before operation and supported after operation by correcting any fluid and electrolyte imbalance, anemia, vitamin, and plasma protein deficiency and impaired function of the heart, liver, and kidneys. The type of operative procedure depends upon the condition of the patient, the location and extent of the growth, and the presence or absence of

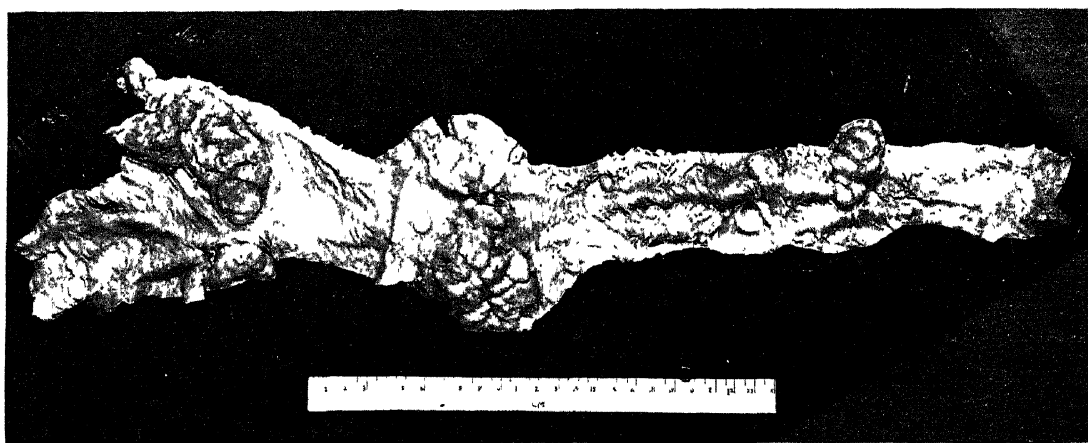


Fig. 6—Multiple polypi of ileum having undergone malignant change. (Shallow, T. A., *et al* : *Am. J. Surg.* 69: 378 (Sept.) 1945)

the severity of the disease and served as a guide in the pre- and postoperative management of the twenty-nine cases with roentgenographic gastrointestinal studies; the lesion was demonstrated in seventeen and suggested in another; the examination was unsatisfactory in two duodenal carcinomas and one extensive sarcoma of the ileum because of vomiting. Eight neoplasms not demonstrated following a complete gastrointestinal examination were one carcinoma of the ampulla of Vater, two carcinomas and one sarcoma of the jejunum, and two carcinomas and two sarcomas of the ileum, even though the duration of symptoms for this group averaged fourteen months.

complications as jaundice or metastasis. Early and adequate resection of the growth and regional mesentery with re-establishment of the continuity of the bowel is the treatment of choice. In this series a variety of surgical procedures was performed. The only duodenal malignancy resected was a carcinoma in the third portion. The third and fourth portions were resected followed by an antecolic side-to-side duodeno-jejunojejunostomy anastomosing the second portion of the duodenum, just distal to the ampulla of Vater, to the jejunum 10 inches from the ligament of Treitz. In the ampullary group, the bile was redirected to the gastrointestinal tract in all cases, but resection was contemplated

in two, without metastasis, had they survived the first stage. All the jejunal lesions found at operation were resected followed by primary anastomosis. One, because of a contact carcinomatous fistula, also required a resection of the terminal ileum followed by an end-to-

end anastomosis of the ileum and ascending colon. Another produced contact sarcoma to the transverse colon, which was also successfully resected and anastomosed primarily. In the ileum, six malignant tumors were resected and primary anastomoses were performed,

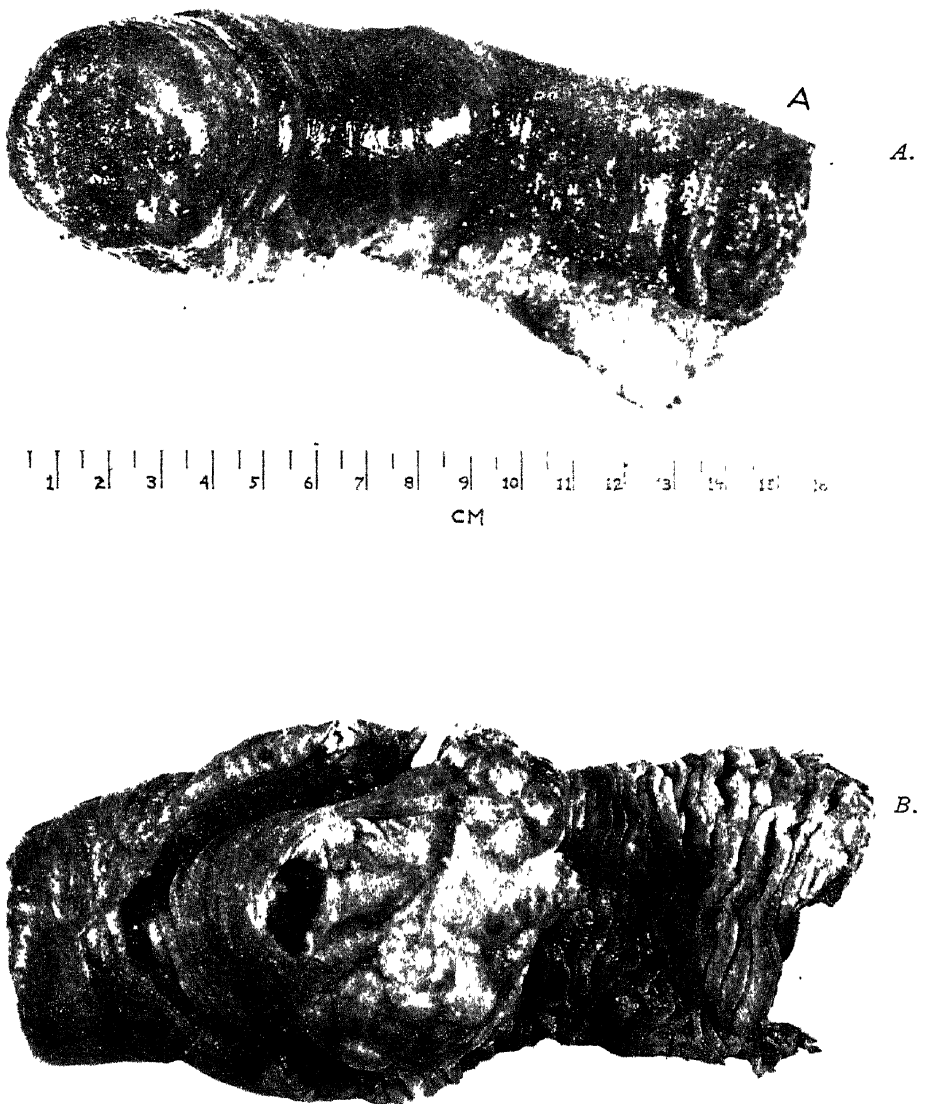


Fig. 7—*A*, Specimen of lymphosarcoma of the jejunum with intussusception producing obstruction. *B*, Opening specimen of lymphosarcoma of the jejunum with intussusception. (Shallow, T. A., *et al.*: *Am. J. Surg.* 69: 379 (Sept.) 1945.)

TABLE I—OPERATIVE PROCEDURES EMPLOYED IN AUTHORS' SERIES

	<i>Duodenum Carcinoma</i>	<i>Ampulla of Vater Carcinoma</i>	<i>Jejunum</i>		<i>Ileum</i>		<i>Total</i>
			<i>Carcinoma</i>	<i>Sarcoma</i>	<i>Carcinoma</i>	<i>Sarcoma</i>	
Resection; side-to-side duodenojejunosomy	1	.	.	.	.	..	1
T-tube drainage of common duct.....	1	.	.	.	.	.	1
Gastroenterostomy ...	1	.	.	.	.	.	1
Cholecystogastrostomy	.	3	.	.	.	.	3
Gastroenterostomy, cholecystojejunostomy	1	.	..	..	..	..	1
Cholecystoenterostomy, Y-type; gastroenterostomy....	..	1	.	.	.	.	1
Cholecystogastrostomy, ligation of common bile duct, gastroenterostomy, enterenterostomy....	.	1	..	..	.	..	1
Resection; end-to-end anastomosis.....	..	.	2	2	1	1	6
Resection; three separate end-to-end anastomoses.....	..	.	..	.	..	1	1
Resection; end-to-end anastomosis with proximal enterostomy	..	.	..	..	..	1	1
Resection; side-to-side anastomosis.....	..	.	2	..	..	..	2
Resection of jejunum and portion of transverse colon, end-to-end anastomoses of each.....	..	..	..	1	..	..	1
Resection of portion of jejunum followed by end-to-end anastomosis; resection of terminal ileum followed by end-to-side ileo-ascending colostomy.....	..	..	1	..	..	..	1
Resection; end-to-side anastomosis of ileum to splenic flexure of colon.....	..	..	..	..	1	..	1
Resection; ileotransverse colostomy, proximal ileostomy..	..	.	..	..	..	1	1
Exteriorization of tumor	..	.	..	..	..	1	1
Exploratory laparotomy	..	..	..	..	1	2	3
Total No. of operations.....	4	5	5	3	3	7	27

(Shallow, T. A., Eger, S. A. and Carty, J. B.: *Am. J. Surg.* 69: 372 (Sept.) 1945.)



another was merely exteriorized and three, not resectable, were administered roentgen therapy.

The results of surgery compare very unfavorably with those for malignancy

of the large intestine. Since small intestinal malignancy metastasizes early and its diagnosis is difficult, it is usually beyond the point of curative resectability when operation is performed.

### An Appraisal of the Results of Surgery in the Treatment of Regional Ileitis

The series of cases to be reviewed includes 164 cases of enteritis, terminal ileitis, and combined ileocolitis. All the cases have been carefully followed for a period of two to fourteen years.

**Analysis of Results—Primary Resection**—A primary resection of the disease process, usually of the pathologic terminal ileum and the adjacent normal ileum and ascending colon, was performed in fifty-five cases. Nine patients died postoperatively. Of the remaining forty-six, nine developed recurrences in the ileum above the point of anastomosis (ileotransverse colostomy or ileosigmoidostomy), a recurrence rate of 19.5 per cent. Some of these recurrences have

TABLE II

OPERATIVE MORTALITY AMONG TWENTY-SEVEN  
PRIMARY MALIGNANCIES OF THE  
SMALL INTESTINE

<i>Location and Type of Neoplasm</i>	<i>No. of Operations</i>	<i>Post-operative Mortality</i>	<i>Percentage Mortality</i>
Duodenum Carcinoma	4	2	50
Ampulla of Vater Carcinoma.....	5	3	60
Jejunum			
Carcinoma.....	5	1	20
Sarcoma.....	3	1	33
Ileum			
Carcinoma.....	3	1	33
Sarcoma.....	7	4	57
Total... ..	27	12	44

(Shallow, T. A., Eger, S. A. and Carty, J. B.:  
Am. J. Surg. 69: 372 (Sept.) 1945.)

TABLE III

END RESULTS OF THIRTY-EIGHT PRIMARY MALIGNANCIES OF THE SMALL INTESTINE

<i>Location and Type of Neoplasm</i>	<i>No. of Cases</i>	<i>Expired without Operation</i>	<i>Duration of Life Following Operation</i>									<i>Living and Well</i>	<i>Lost to Follow-up</i>
			<i>1 Wk.</i>	<i>1 Mo.</i>	<i>3 Mo.</i>	<i>6 Mo.</i>	<i>1 Yr.</i>	<i>3 Yr.</i>	<i>4 Yr.</i>	<i>15 Yr.</i>			
Duodenum Carcinoma													
Supra-amp.....	3	2	..	1									
Peri-amp.....	3	1	1	1									
Infra-amp.....	1	..	..	..	..	..	..	..	..	..	1 (10 mo.)		
Ampulla of Vater Carcinoma.....	7	2	3	..	..	..	1	..	..	..	..	..	1
Jejunum Carcinoma...	5	..	1	..	..	1	..	1	1	..	1 (4 yr.)		
Jejunum Sarcoma...	6	3	1	..	..	..	..	..	..	1	1 (12 yr.)		
Ileum Carcinoma.....	5	2	..	1	..	..	..	..	..	..	..		2
Ileum Sarcoma...	8	1	3	1	1	1	..	..	..	..	1 (7 yr.)		
Total.....	38	11	9	4	1	2	1	1	1	1	4		3

(Shallow, T. A., Eger, S. A. and Carty, J. B.: Am. J. Surg. 69: 372 (Sept.) 1945.)

not been severe, and, except for diarrhea and some loss of weight, the patients have been treated medically in a fairly satisfactory manner. The fact that the authors<sup>7</sup> (Garlock and Crohn) have encountered no late mortality in this group indicates that, once the risk of immediate operation has been overcome, life itself is assured, although physiologic intestinal function of general weight, strength, and efficiency may be impaired. The larger incidence of recurrence not hitherto recognized is due in large part to the longer period of follow-up. In this group they noted a case of recurrence eight years after the original observation and another instance of recurrence twelve years after the first surgical procedure. In both instances, eight to twelve years of perfect health and function intervened between the primary operation and the severe recurrence. In this group the primary operative mortality rate is appreciable (16.3 per cent), but late follow-up studies show a distressingly high rate of recurrence.

**Ileocolostomy Group**—An ileotransverse colostomy or ileosigmoidostomy with transection of the ileum was carried out in sixty-five cases with no operative death. Nine recurrences of the disease must be recognized, a recurrence rate of 13.8 per cent.

**Two-Stage Ileocolic Resection**—This graded type of operation consists of a primary short circuiting ileocolostomy above the lesion with transection of the ileum followed after a period of time by resection of the original area of disease in the terminal ileum and cecum and ascending colon. There were twenty-five patients in this group, with three postoperative deaths, a mortality of 12 per cent. They noted eight instances of recurrent disease in the surviving twenty-two patients, a rate of 36.3 per cent. The second of these two-stage proce-

dures was often necessitated by the lack of success of the first or short circuiting operation. The operative risk was, therefore, greater and the likelihood of recurrences similarly enhanced in spite of the second more radical procedure. In the combined cases of ileocolitis in which the ileum and same segment of the colon, usually ileum and cecum or ileum and ascending and transverse colon, are involved, the magnitude of the surgical procedure or procedures is greater, the risk is increased, and the results more dubious. Nineteen cases of combined ileocolitis are included in this group. There were two operative deaths and three instances of recurrence of the disease. Included in this series are two cases of multiple resections of the ileum for concomitant disease in two widely isolated segments of the small bowel. One patient is well and one developed a recurrence.

**Operative Mortality**—In the entire group of 164 cases, regardless of the complexity of the procedures involved, there were 14 deaths, an operative mortality of 8.5 per cent. The low operative risk for intra-abdominal procedures of such magnitude bespeaks the successful advances in surgical judgment, technic, anesthesia, and preoperative and postoperative care.

**The Choice of Operation**—The authors have collected enough material to permit an evaluation of the relative merits of primary resection as compared with short circuiting procedures. They noted fifty-five primary resections with nine operative deaths and a recurrence rate of 19.5 per cent. In comparison, they had sixty-five short circuiting procedures with no operative death and a recurrence rate of 13.8 per cent. The greater safety of the less radical procedure and its smaller rate of recurrence would weigh the balance strongly in

favor of the more conservative operation. Is it correct to term an ileotransverse colostomy or an ileosigmoidostomy with transection of the ileum a "palliative procedure"? "Palliative" would indicate an incomplete or a temporary measure, short of permanent cure. Such a term as applied to a short circuiting procedure for the relief of regional ileitis is a misnomer, for in the course of the twenty-five instances in which a two-stage resection was undertaken the specimen, when finally removed after a variable interval, showed in almost every case complete healing. In the interval between the two operations, abdominal inflammatory masses rapidly dissolve, abdominal wall fistulas heal and enterovesical communications close spontaneously. The resected specimens show advanced healing, scar replacement, a shrinkage of the lumen of the intestine and cessation of evidence of inflammation. Why, then, was the second-stage or resection undertaken? Either because the two-stage procedure had been planned and adopted as the operation of choice and was carried through as per schedule because, in the judgment of the surgeon, conditions warranted the completion of the assignment, or persistent diarrhea or some localized discomfort or pain in the restoration of full weight and strength seemed to indicate the removal of an area which might be a residual focus of disease. Also, because of the not infrequent recurrence above the anastomosis, it was originally thought that the secondary removal of the original source of infection would reduce the incidence of recurrences. The two-stage operation has been generally discarded for three reasons: (1) Because in most instances the resected area of ileitis was found inactive and healed and fistulas spontaneously closed; (2) because in spite of the second stage

resection the percentage of recurrence remained as high, if not higher, than following the simple short circuiting procedure, and (3) because in the group of the twenty-five cases of two-stage resections the authors noted three deaths, an appreciable mortality.

**The Question of Recurrence**—It is difficult to explain satisfactorily the relatively high rate of recurrence proximal to the new anastomosis. Two possibilities immediately suggest themselves: Either the surgeon is unable to recognize the most proximal of the skip lesions before transecting the ileum, or the recurrent focus starts from a nidus of infection outside of intestinal wall proper. With increasing experience, the surgeon should be able to demonstrate all skip areas, knowing that these are characteristic features of the disease. This demands, in every case, a careful examination at the operating table of the entire small intestine. It is possible, however, that some skip areas may be so small as to escape the attention of the most experienced and alert technician. If this is the explanation, then a much wider area of small intestine must be excluded in order to circumvent any inclusion of disease above the anastomosis, a decision which might invite serious diarrhea and nutritional disturbances because of too much exclusion of mucosal absorbing surface. It has been suggested that the recurrences are due to residual infection outside the intestinal wall, the main suspicion being directed to the mesenteric lymph nodes. The fact that the recurrence rate is just as high, if not higher, after radical resection with excision of the mesenteric lymph nodes would seem to imply that these lymph nodes are not responsible for the recurrences. It must be emphasized further that secondary operation, on many occasions, has disclosed complete recession

of previously enlarged nodes after a simple ileocolostomy.

**The Clinical Significance of Recurrence**—The diagnosis of recurrence is suggested by the presence of diarrhea, fever, and loss of weight and is confirmed by radiographic demonstration of irregularity in the segment of ileum proximal to the new anastomosis. This is best demonstrated by the barium enema. In many of these so-called recurrences, the basis for such a diagnosis is the roentgenographic demonstration of a distorted mucosal pattern or irregularity of outline of the "new" terminal segment of ileum. These patients do well with general supportive measures, such as diet, rest, liver extract, and vitamin B injections, and they often improve with *succinylsulfathiazole* or *sulfathalidine* as chemotherapeutic agents. A large number of patients suffering with mild recurrences of the radiographic type have been under observation for some years and remain comparatively well.

No satisfactory medical treatment of ileitis exists. Until the cause of the disease is discovered, the treatment of ileitis remains surgical.

### Treatment of Carcinoma of Colon

In the treatment of carcinomas of the colon in this series of 173 patients, Collier and Vaughan<sup>8</sup> have endeavored to perform resection with primary anastomosis whenever feasible. In this series they have used the open methods in 52 patients and the closed or aseptic method in 68 patients. Generalized peritonitis occurs from persistent leak of an anastomosis, severe wound infection, or as a result of contamination by rare virulent organisms. The striking point of difference between the two methods is not that peritonitis is more apt to occur with one method or the other, but that with any open anastomosis, there is a

high risk of contamination of the abdominal wall with an increased risk of infection at that place. The peritoneum will withstand infection much better than will the abdominal wall.

They used delayed closure of the abdominal wound whenever open anastomosis has been used, whenever there has been gross soiling from the gastrointestinal tract, and in closure of colostomies or other fistulous openings in the gastrointestinal tract with satisfactory results. There was a resultant infection in 8.4 per cent, but these were all minimal. The chief point in favor of an aseptic form of anastomosis is that the wound may be closed primarily; if the open method is used, one should assume that the wound in the abdominal wall is contaminated, and delayed closure should be employed. In performing the closed type of anastomosis they have used clamps with a narrow blade, employing an outer layer of silk mattress sutures and an inner suture of fine catgut inserted by the Cushing right-angle method. Clamps are applied at a right angle, unless there is a discrepancy in the size of the lumen of the two segments. The bowel wall must have an adequate blood supply and be approximately normal in its histologic state if primary suture is carried out; tension must never be present; the bowel is never dissected from its appendages or mesentery in order to secure cleared serosa for approximation. The peritoneum covering the mesentery and the appendages will unite when approximated if the blood supply is undisturbed. The anastomosis is supported by peritoneal flaps and the omentum whenever possible.

In the closure of colostomies, the authors have abandoned the use of crushing clamps applied to spurs. The colostomy is freed from the abdominal wall, and appropriate end-to-end anas-

tomosis is made, the abdominal wall being closed by the delayed method. Stenosis of the bowel may occur following the contraction of the scar of a primary anastomosis. In three patients in this series, this did eventuate a year or more after operation as shown by roentgenologic studies.

Preoperative decompression is employed whenever obstruction is present. If rapid relief from distention is desired, cecostomy is performed; if it is thought that the colon is filled with solid contents and evacuation will be difficult and if the colon is not greatly distended, a colostomy is carried out. They do not routinely defunctionalize the left colon by transverse colostomy before performing end-to-end anastomosis in that organ. In those cases in which obstruction was not present and upon whom resection with end-to-end anastomosis was carried out, a complementary cecostomy was performed in all but six patients and a cecostomy was performed following operation on one of these because of distention. Cecostomy or colostomy before operation is necessary in obstructing lesions; complementary cecostomy adds to the comfort of the patient and is a worth-while safeguard. The great majority of these closed spontaneously within a short time following removal of the catheter.

The *sulfa drugs* were used locally and generally in a few patients treated in the early cases of the series. They have not been used locally in any cases operated upon since July, 1940, and they have been used generally only in those patients with peritoneal, urinary, or pulmonary infection. *Sulfaguandine* and *sulfasuxidine* were used as a preoperative measure in a few cases but they have not been used as a routine.

*Succinylsulfathiazole* and *Phthalylsulfathiazole* in Surgery of the

**Colon**—In 1941, *succinylsulfathiazole* (sulfasuxidine) was introduced by Poth and Knotts (1941) as an intestinal anti-septic. The drug has found rather widespread use as an agent to modify the bacterial flora of the colon and to prepare this section of the bowel for surgery. The antibacterial action of the compound effects a considerable drop in the grain negative flora of the bowel. Both aerobic and anaerobic organisms are affected. Before sulfasuxidine is administered, the colonies of coliform organisms on the plate count has dropped to 100, the feces being studied will contain roughly 10,000 coliform organisms per gm. The authors' practice has been to consider a coliform population not exceeding 1000 organisms per gm. of feces or indicating a satisfactory preoperative preparation of the colon, and the corresponding count on the streaked plate should not exceed twenty colonies.

In 1943, Poth and Ross published their results in a continued study of the acylated sulfonamides and presented data on *phthalylsulfathiazole* (sulfathalidine) which showed this compound to possess approximately twice the bacteriostatic activity shown by sulfasuxidine as indicated by their antibacterial actions against the coliform organisms in the gastrointestinal tract of dog and man.

In general, the effects of sulfasuxidine and sulfathalidine are similar, as indicated by their antibacterial action against the coliform organisms. Sulfathalidine does not tend to reduce the feces to a semifluid state, nor does it effect as great a degree of change in the odor of the stools. Sulfathalidine has the greater tendency to alter the coliform count and will lower the count even in the presence of severe diarrhea. The feces tend to become tenacious and stringy and result in less efficient mechanical empty-

ing of the bowel and a less satisfactory surgical preparation unless enemas and purgatives are used simultaneously.

**Dosage**—Since sulfathalidine has twice the bacteriostatic activity of sulfasuxidine, one half the amount of the former drug would have a bacteriostatic action, as indicated by the effect on the coliform organisms, equal to that of the latter compound. The usual dosage of sulfasuxidine is 0.02 gm. per pound of body weight every four hours, or 3.0 gm. every four hours for an average-sized man (150 pounds). This dosage is approximately 0.25 gm. per kg. each twenty-four hours. The corresponding dose of sulfathalidine is 1.5 gm. every four hours.

**Toxicity**—Of the several thousand individuals who have received these drugs in full therapeutic doses, there has been but a single fatality reported due to drug intoxication following the administration of sulfasuxidine. Clay and Pickrell (1943) reported two reactions following succinylsulfathiazole administration. Poth<sup>9</sup> has observed two instances in which patients developed myalgia, arthralgia, hyperpyrexia, and a rash following the administration of sulfasuxidine. Mild reactions to both drugs are not infrequent, and an occasional severe reaction must be expected. Ordinarily, these reactions consist of nothing more severe than headache, malaise, anorexia, and moderate rise of temperature and do not require that the therapy be interrupted. Of the two drugs, sulfathalidine, is the least toxic. Any patient receiving either of these drugs should be under adequate observation. Allen<sup>10</sup> reported that approximately one fifth of his patients having carcinoma of colon showed increased hemorrhage after receiving sulfasuxidine for four or five days.

**The Preoperative Preparation of the Colon**—Not only is it desirable to lower the bacterial count and simplify the flora of the bowel before operation, but the colon must be mechanically clean and empty. Ordinarily these conditions can be accomplished by merely placing the patient on a low residue diet and administering sulfasuxidine. Most surgeons insist upon using purgatives and enemas as a part of the surgical preparation. In this event, and in the absence of obstruction, the patient is placed on a residue free diet high in protein and carbohydrate, a saline purgative is given to effect efficient evacuation of the bowel by several watery stools, after which a high colonic flush is administered. The diet should consist of strained fruit juices fortified with lactose, gelatin, casein, jello, and vitamin concentrates. A minimum of 100 gm. of protein should be taken daily, especially if the patient has been on a restricted protein intake. Occasionally a malnourished patient will not respond to an adequate protein intake. Only the simplest emergency operation should be done when the plasma protein concentration is less than 5.5 per cent and the A-G ratio is less than 1.5. These patients may require amino acids intravenously for three to five days.

**The Use of Sulfasuxidine for Preoperative Preparation**—Sulfasuxidine, 3.0 gm., is given orally every four hours for at least seven days if no observations are made on the coliform content of the feces. In the presence of a watery diarrhea, 3.0 gm. of sulfathalidine each four hours should be substituted for the sulfasuxidine. Should the diarrhea stop, the dosage should be reduced to 1.5 gm. of sulfathalidine. If an enema is given on the evening preceding operation, it should consist of sterile tap water containing 10.0 gm. of sodium bicarbonate and 6.0

gm. of sulfasuxidine powder to the liter administered as a high colonic flush in sufficient quantity to insure complete evacuation of the colon. Sulfasuxidine appears to be slightly irritating to the mucous membrane of the large bowel resulting in an increased secretion of mucous characteristically accompanied by three or four small soft bowel movements daily.

***The Use of Sulfathalidine for Preoperative Preparation***—Sulfathalidine, 1.5 gm., is given orally every four days for at least seven days if no observations are made on the coliform content of the feces. If the coliform content is observed using the streak method, the therapy is continued until the number of coliform colonies on the streaked plate is less than twenty. This observation will frequently allow a considerable reduction in the time required for satisfactory preparation, because many patients will have shown a significant alteration of the bacterial flora in these three days of therapy. Sulfathalidine is not as efficient as sulfasuxidine in effecting mechanical cleansing of the bowel, because it does not render the feces as fluid. Mild purgation must ordinarily be used in conjunction with the administration of phthalylsulfathiazole. The patient should have at least one bowel movement daily. Should the patient develop a diarrhea, the dosage of sulfathalidine should be doubled. If enemas are used, they should consist of sterile, warm, tap water containing 10.0 gm. of sodium bicarbonate and a suspension of 6.0 gm. of sulfathalidine powder to a liter. In the presence of fecal fistulas diverting the fecal stream away from the distal portion of bowel, not only must the usual dose of drug be given by mouth, but an equal quantity of drug must be introduced into the distal segment of bowel if the flora in this portion is to be affected. It is not

universally agreed that sulfasuxidine is the drug of choice for the preoperative preparation of the colon, and it certainly would not be so if a watery diarrhea exists or if enemas and purgatives are administered. Sulfathalidine will likely be preferred by many surgeons, because its greater antibacterial activity will prevent the use of purgatives and enemas. Poth avoids the use of any procedures accessory to the administration of either sulfasuxidine or sulfathalidine, and considers sulfasuxidine to be superior. Bargen,<sup>11</sup> on the basis of experience gained from the observation of 2075 patients treated with sulfasuxidine and sulfathalidine states: "Sulfasuxidine, so far, has proved to be the drug of choice in preoperative management, with sulfathalidine serving as an alternative when toxicity to sulfasuxidine manifests itself." It is unnecessary, routinely, to determine the level of these drugs in the blood, because only about 5 per cent of the ingested drug is observed and the rate of excretion by the kidneys is rapid. In the event of an outward reaction, the blood level should be determined.

***The Postoperative Administration***—There may be little indication for the postoperative administration of these locally active sulfonamides; for example, when the operative procedure ends in a colostomy as in the case of an abdominoperineal resection. When bowel suture is performed, however, and the involved segment is retained in the peritoneal cavity, the bacterial flow should be controlled for twelve days postoperatively so as to pass the period during which leakage may occur at the suture line. After the first twenty-four hours, the patient can tolerate water by mouth in 30-cc. quantities at hourly intervals with 1.5 gm. of sulfathalidine every four hours. It is best to give a single 0.5-gm. tablet of drug on three occasions

during the four-hour interval rather than the entire drug in a single dose.

**Submucous Lipomas of Colon with Special Reference to Acute and Chronic Intussusception**—Lipomas involving the bowel occur as subserous or submucous tumors, the latter being the more frequent.

**Pathology**—Submucous lipomas belong in the category of true lipomas, and, as far as can be ascertained, are never congenital in origin. The tumor is, in the vast majority of instances, polypoid, well circumscribed and encapsulated, either sessile or pedunculated, and usually occurs singly, although cases of multiple lipomas have been reported. The tumor shows no tendency to assume malignant propensities, although it is prone to undergo a variety of intrinsic alterations, such as hemorrhage, cystic degeneration, inflammatory changes, or necrosis. The mucous membrane covering the tumor is usually atrophied and scarred, although it may be hypertrophic. Instances have been reported in which the mucosa had completely sloughed off over the growth. The tumor originates from the fat cells in the connective tissue stroma of the intestinal submucosa. Submucous lipomas are slightly less frequent than adenomatous polyps, but in comparison to carcinoma they are extremely rare.

**Symptomatology**—In many instances, the condition is asymptomatic, particularly when tumors are small (11.6 per cent). Large tumors, however, are always associated with symptoms. Depending upon the character and size of the growth, and the condition of the bowel wall harboring it, the presenting symptoms may be chronic or acute. In chronic cases, the patient may complain of vague abdominal pains, intermittent or continuous. At times the pain may be colicky or diffuse, and frequently

localized to the site of the tumor, where it may be mistaken for other intra-abdominal disorders such as cholecystitis or appendicitis. Constipation is an outstanding symptom, and is often associated with diarrhea. When associated with partial invagination of the involved portion, and when the lumen of the bowel is materially reduced, chronic obstipation may occur. Stools frequently contain mucus, blood or pus, or all three, depending upon the degree of degeneration of the tumor. Large tumors may occasionally be felt through the abdominal wall, particularly in thin patients. When situated in the rectum, they can almost always be detected on rectal digital examination, regardless of size.

Acute syndromes result from acute intestinal obstruction, due most frequently to intussusception or occasionally to complete obstruction from the tumor itself without intussusception. In the authors'<sup>12</sup> series, 45 per cent were associated with intussusception. The tumor has always been found situated at the tip of the intussusception. When the growth is situated in the rectum, the patient usually complains of tenesmus and constipation. Blood and mucus are frequently found in the stool.

**Prognosis**—In this series, fourteen patients (11 per cent) expelled the tumor spontaneously and went on to eventual recovery. The remaining patients developed acute symptoms and required surgery. In the latter group, the mortality rate was 11 per cent.

**Treatment**—In chronic cases in which the identity of the tumor can be established presurgically, the best treatment is colostomy with extirpation of the tumor. However, when the identity of the growth is uncertain, it is best to perform resection of the involved portion of the colon. When acute, surgery is urgently indicated. Tumors unassociated



with intussusception are best treated by colostomy with removal of the growths when their precise identity is known before operation. When intussusception is present, it should be reduced whenever possible, and the tumor removed after opening the bowel. In instances of irreducible intussusceptions, several procedures are available. The bowel may be opened and the intussusception removed at its base; or the entire involved portion may be resected and the continuity of the bowel restored by end-to-end or side-to-side anastomosis. An even safer operation is the exteriorization procedure of Mickulicz. However, when a patient's condition is such as to preclude radical surgery, simple enterostomy should be carried out proximal to the obstruction and radical resection of the involved portion of the bowel performed at a later date when his condition has improved sufficiently to enable him to safely withstand such an ordeal. Rectal tumors are best treated by extirpation after manually reducing the invagination when present.

#### **Volvulus of the Sigmoid Colon—**

At the Cook County Hospital, 458 cases of large bowel obstruction were treated between 1937 and 1945. Thirty-seven of these cases were volvulus of the sigmoid colon. Griffin *et al.*,<sup>13</sup> basing their report on twenty-five cases, made the following observations: Fourteen cases, or 56 per cent, were confined to the age group of fifty-one to seventy years. Sixteen were males and nine females. Their cases fit into two general types, acute and subacute. Seven patients of the acute type, or 28 per cent, which occurred in the younger age groups, had an onset that is short in duration, usually about twenty-four hours, with no history of previous attacks and an equivocal history of constipation. All these patients experienced early emesis of a transient

nature, and generalized cramping abdominal pain. Eighteen patients of the subacute type, or 72 per cent, showed a different picture in that the condition occurred in the older age groups, had a more gradual onset of symptoms, with an average duration of 102 hours, and consistently presented a history of previous attacks, chronic constipation, emesis late in the course of the disease, and cramping lower abdominal pain.

**Physical Findings—**Half of the acute type showed distention, audible peristalsis, minimal abdominal tenderness, and ability to take amounts of enema up to 1000 cc. The x-ray films in these patients indicated distention of the sigmoid due to volvulus, and laparotomy revealed a sigmoid volvulus with viable bowel. The remainder of the acute type had severe distention, absence of peristaltic sounds, abdominal tenderness, and the inability to take more than a 500-cc. enema. The flat film of the abdomen or the barium enema revealed a pattern indicative of volvulus of the sigmoid. Laparotomy confirmed these findings and showed, in addition, a gangrenous loop of bowel. The two deaths which occurred in the acute type had developed a gangrenous segment.

All the cases of the subacute type of sigmoid volvulus were characterized by severe abdominal distention. Marked tympany and audible or visible peristalsis were also absent. Abdominal tenderness was a variable finding. The enema test was for the most part consistent in that 76 per cent of the patients were unable to take more than a 500-cc. tap water enema introduced under the force of gravity. The patients who were able to take more than 500 cc. were in the class of incomplete volvulus and the enema return was always incomplete as some of the solution was caught in the twisted loop. It was seldom necessary

to use the barium enema to make the diagnosis. However, in those few cases in which, on examination of the gas pattern on the flat film of the abdomen, doubt still existed as to the diagnosis, the pattern of the barium enema was conclusive. Gangrene was present in half of the cases of the subacute type. The mortality rate was 50 per cent but was unrelated to the gangrene, since an equal number succumbed with a viable bowel as with a gangrenous bowel. The over-all mortality for both types was 40 per cent.

The acute type follows the course of a fulminating lesion, and there is the same marked prostration that is associated with volvulus elsewhere in the gastrointestinal tract. Because all of these patients have early transient emesis, cramping abdominal pain with tenderness in all the quadrants of the abdomen, and some fever, their symptoms may be mistaken for an inflammatory intra-abdominal lesion. The great majority of the patients with subacute sigmoid volvulus were ambulant throughout the course of the disease despite the tremendous distention of their abdomen and a complaint of only moderate discomfort. The symptoms are at first attacks of partial obstruction of the colon. Obstipation for a day is followed by a distended abdomen and gas pains below the navel relieved by flatus. The tendency is for the attacks to become more frequent until complete obstruction sends the patient to the physician.

**Treatment** — Eight patients were treated by a Mickulicz procedure. Of these, six were treated by this method as the initial procedure. One patient had a cecostomy fifteen days previously, and one patient had a simple detorsion, then a recurrent attack and a lateral anastomosis, and, on the third recurrence, an exteriorization and resection

of the redundant sigmoid loop. Three patients expired and in all three gangrenous bowel was present. Six patients were treated by a simple detorsion with one death. Of these, three patients had recurrent attacks; one of which was relieved by conservative therapy, one by a lateral anastomosis between the proximal and distal segment loops, one patient was not relieved by conservative therapy and expired. Five patients were treated by a Rankin obstructive resection with a fatal outcome in three. In four patients the diagnosis of large bowel obstruction was made and they were treated by a McNealy cecostomy. They did not respond to this therapy. Two patients died and of the two who survived cecostomy, one required a Rankin obstructive resection twenty-four hours later for gangrenous bowel, and the other was partly relieved by the cecostomy only to become completely obstructed, requiring an exteriorization procedure fifteen days later. Two patients were treated by conservative methods of oil and enema routine in the knee-chest position because they refused operation. One of these recovered but he had a recurrence of his volvulus two years later and expired. One of the most significant findings in this review of the operative and nonoperative therapy of volvulus of the sigmoid colon is that volvulus is a lesion with a marked tendency to recur, doing so in 20 per cent of the cases and necessitating further operative procedures and being associated with a mortality of 40 per cent.

**Surgery in Obstinate Megacolon** — The literature review has demonstrated that protracted medical treatment of megacolon on Hirschsprung's disease may be associated with a high mortality. Surgical intervention is indicated when medical management fails and recurring episodes of serious impaction and ob-

struction or persistent and progressive abdominal distention develop. Sympathectomy, although it may occasionally facilitate medical management, does not appreciably alter the gross pathology. Reports of volvulus or impaction and perforation after sympathectomy are accumulating and are attributed in the literature to an overactivity of the large inert colon. The authors<sup>14</sup> believe that the interruption by sympathectomy of the visceral pain pathways that warn patients of impaction and impending danger and provoke strenuous evacuation efforts is a more reasonable explanation of these accidents. Colostomy or cecostomy may be indicated for temporary relief in the occasional patient. Usually, however, colon evacuation may be accomplished by persistent medical efforts. Segmental colon resection is not uncommonly followed by a recurrence of symptoms of dilatation and impaction in the remaining colon. More radical colon resection would seem indicated if practical.

Three types of megacolon pathology have been encountered by the authors. The patients of Group 1 with uniform enlargement of the colon and rectum respond well to medical treatment and only occasionally develop difficulty. Should colon resection be indicated in patients of this group, resection of proximal segments of the colon and ileosigmoidostomy would empty liquid bowel content into the remaining enlarged bowel and diminish the danger of recurrence of impaction. Patients of Group 2 with uniform enlargement of the proximal colon and sigmoid, and a normal segment of lower sigmoid and a normal rectum respond poorly to conventional management. Megacolon resection when indicated in patients of this group may be complete. Bowel continuity may be established by an anastomosis between terminal ileum and the segment of nor-

mal sigmoid colon. Patients of Group 3 with immense involvement of the upper sigmoid and occasionally the descending colon apparently respond favorably to protracted medical management.

### **Roentgenologic Examination of the Abdomen as an Aid in the Early Diagnosis of Splenic Injury**

Damage to the spleen is probably the most common serious intra-abdominal injury resulting from blunt force. Clinically, three types of bleeding may occur: (1) Extensive rupture with immediate massive hemorrhage; (2) small lacerations which ooze blood slowly over a period of hours or possibly days, and (3) delayed splenic rupture. Delayed splenic rupture occurs in about 14 per cent of all splenic injuries. The second and third types of splenic injuries are difficult to diagnose in the hours immediately following trauma, especially in the presence of associated injuries. The patient's symptoms and signs may disappear completely or so improve that he may be allowed to resume full activity. Then, after a latent period of hours, days, or even months, secondary hemorrhage may occur, usually of such severity that circulatory failure ensues rapidly. The time to remove a slowly bleeding spleen is early, before blood loss threatens life, and the ideal method of handling a delayed rupture of the spleen is to perform splenectomy early. Diagnosis must, therefore, come early, and yet the difficulties of such early diagnosis are great. There is evidence that the roentgenologic examination of the abdomen can be of great aid in establishing early the diagnosis of a lacerated spleen. Webb (1940) reported increased density in the left upper abdominal quadrant, with elevation of the left side of the diaphragm, displacement of the

stomach to the right, and free fluid between loops of intestine. Zabinski and Harkins (1943) mention elevation of the diaphragm in one patient and medial displacement of the colon in another. They also mention Bancroft's experience in administering barium sulfate to a boy, placing him in the Trendelenburg position, and observing a mass in the region of the spleen displacing the stomach. The roentgenographic findings described by Solis-Cohen and Levine<sup>15</sup> may answer the need for a reliable, simple means which will aid in the early diagnosis of minimal to moderate or severe splenic damage. These authors, in making roentgenologic examinations of the abdomen in three patients suspected of having splenic injury, described obliteration of the splenic shadow, and a dilated stomach, with serration of the greater curvature.

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## NEUROSURGERY

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### Diagnostic and Therapeutic Technics

**Cerebral Arteriography** — List and his colleagues<sup>1</sup> discuss intracranial angiography. In the first three years they have subjected 127 patients to this type of examination. In the bulk of these, the carotid system was injected; vertebral arteriography was used in only six instances. They emphasize the fact that when the indications for its use are clear, this technic may be employed without danger to the patient if certain conditions are observed. They feel it is inadvisable to inject any material into the circulation of the brain in cases of extreme arterial hypertension, far advanced arteriosclerosis, acute intracerebral or

subarachnoid hemorrhage, recent thrombosis, or embolism of cerebral vessels. Even in the absence of such contraindications one may occasionally encounter transient hemiparesis, hemiparesthesia, aphasia, convulsive manifestations, or temporary accentuation of presenting neurologic signs. Such untoward effects occurred in less than 3 per cent of the patients examined by the authors, and in no instance did they persist. Actually angiography is better tolerated than ventriculography in certain cases of expanding lesions associated with high intracranial pressure because intracranial hydrodynamics are not materially altered. The authors adopted a procedure of exposing the internal carotid for injec-

tion in that they felt that this approach allowed them to inject the total amount of contrast material needed. Despite its undesirable property of long half-life radioactivity, thorotrast in amounts not exceeding 25 to 30 cc. was the contrast medium utilized. Lowman and Doff<sup>2</sup> report their experiences with arteriography for the demonstration of intracranial aneurysms. They felt that the injection of the common carotid will not satisfactorily demonstrate the cerebral arteries, since blood and the contrast medium will be shunted through vessels which do not directly supply the cerebral hemispheres. Therefore they advocate the section of the internal carotid on the side of the suspected lesion with introduction of the contrast medium under direct visualization. The authors utilize a 50 per cent solution of diodrast compound as described by Gross (see last year's Service Volume). They used thorotrast in the injection of thirteen of their cases. They describe the technic employed in detail. They emphasize arteriography will often reveal the presence of an aneurysm when other studies previously performed will have failed to do so.

**Myelography**—Soule and his co-workers<sup>3</sup> report their experience in the diagnosis of herniations of the intervertebral discs by the use of pantopaque myelography. Their technic for the introduction and removal of pantopaque is described and is substantially the same as that described by Kubik and Hampton for lipiodol myelography. The patient lies prone on a roentgenoscopic tilt-table equipped with a spot film device, his feet braced against the foot rest, a rolled pillow under the abdomen to arch the lumbar spine. The head of the table is elevated about 10° to 15° above horizontal. Under ordinary aseptic precautions, a No. 18 gauge spinal needle is

inserted at the third lumbar interspace, care being taken to make a central puncture. The third lumbar interspace is chosen (even though subsequent removal is slightly more difficult) because of the relative infrequency of herniations at this level. Since most lumbar disc herniations occur at the fourth or fifth interspace, a false defect due to a needle puncture at these levels is avoided. After ascertaining that the needle is within the subarachnoid space, 3 cc. of pantopaque is injected slowly; the obturator is replaced, and the area is covered with a sterile towel. The pillow is removed from beneath the abdomen and placed under the patient's legs. The fluoroscopic screen is drawn into place and a supporting bar of wood is placed under the arm of the screen to prevent it from dropping and hitting the needle. Bars of several different lengths should be available for use with patients of varying size. By tilting the table, the pantopaque is allowed to flow from the caudal sac to the highest level under study. The pantopaque should be passed over any suspicious area several times. Filling of the nerve root sheaths is facilitated by rolling the patient slightly from side to side. Any lag, delay, or deviation in the course of flow of pantopaque should be observed. As noted by Copleman, the head of the column should be scrutinized carefully in the anteroposterior and oblique projections, as small central defects may otherwise be overlooked. If the spinal canal is unusually wide or if doubt exists as to the demonstration of a lesion, an additional 3 cc. of pantopaque may be injected. The range of motion of the tilt-table is sufficient to allow for study of the lumbosacral canal of the average patient. Occasionally it is necessary to place a pillow under the pelvis in order to tilt the spine sufficiently to fill the upper lumbar canal.

The same effect can be produced by having the patient elevate his pelvis several inches from the table, care being taken that the needle does not hit the fluoroscopic screen. Spot roentgenograms are taken of each lumbar disc. The pantopaque then is pooled opposite any suspicious area and a posteroanterior Bucky roentgenogram is taken on a 10 by 12-inch film. This larger film gives a reverse projection of the canal from that observed roentgenoscopically and offers added evidence regarding the area under study. It is also useful to the surgeon as it outlines the defect in relation to the lower spine. Oblique and lateral projections are of help in occasional cases. The latter are produced by directing the coned rays laterally through the spine with the patient lying prone on the table, the pantopaque pooled opposite the area under study. A wafer grid over the cassette improves details. Following completion of study, the pantopaque is pooled about the needle point under roentgenoscopic control and is withdrawn by gentle suction. If a nerve root is drawn against the needle point, thus producing pain, rotation of the needle usually will move it away. Occasionally it is necessary to insert a second needle at the fourth or fifth disc level where the pantopaque is withdrawn more readily than at the higher interspaces. Pantopaque myelography was employed as a diagnostic procedure in forty-eight patients. They conclude that this procedure should precede exploration in nearly every case for the following reasons: (1) It offers objective evidence as to the presence of a lesion. It should be noted, however, that negative findings do not exclude the presence of herniations lateral to the limits of the subarachnoid space, which are found in a small minority of cases. (2) It localizes the lesion and provides valuable information regarding the pres-

ence or absence of multiple herniations. (3) The procedure is a simple, safe, and nearly painless one. (4) If pantopaque is left in the subarachnoid or epidural space there is evidence that the retained substance is nonirritant, nontoxic, and is absorbed slowly. (5) While the operation for removal of a herniated disc is not formidable, it is sufficiently serious so that all information possible should be available before it is undertaken. They have encountered no untoward sequelae or complications referable to myelography with pantopaque. They are of the opinion that myelography should be done in nearly every case of low back pain with sciatic radiation before the patient is subjected to a fusion operation on the spine or sacroiliac joints.

Peacher and Robertson<sup>4</sup> report their results with pantopaque myelography in 300 successive cases. Its accuracy in diagnosis was 96.7 per cent in 150 cases operated upon for herniated nucleus pulposus. In fluoroscopy and x-ray interpretation, pantopaque is comparable to lipiodol, but it is unlike the latter in that it is easily removed, is gradually absorbed, reactions are extremely rare, it is not contraindicated in the presence of inflammatory or degenerative lesions, and it has not resulted in encystment. Further, the meningeal response to injection has been minimal and transient. Symptoms of meningeal irritation may occur after an interval if pantopaque extends into the basal cisterns. Tarlov<sup>5</sup> reports a case of pantopaque meningitis disclosed at operation. Signs of meningeal irritation occurred five hours after 3 cc. of pantopaque was injected intrathecally.

**Cranioplasty**—Woolf and Walker<sup>6</sup> review the subject of cranioplasty in detail. They point out that perhaps the most astonishing finding in a review of cranioplasty is the great tolerance of

human tissue for foreign bodies. This undoubtedly is the reason that so many different types of grafts have been suggested and used for repair of the skull with successful results. There is no doubt that the alloplastic grafts (metal or plant-alloplastic graft) can be molded to a more complex contour to produce a cosmetic result superior to that obtained by other types of grafts. Such shaping of the graft is especially necessary in the frontal region and for defects in this region alloplastic grafts are particularly desirable. For defects in other parts of the skull where the cosmetic results are not so important, the advantage of alloplastic cranioplasty may not be so evident. The somewhat simpler and shorter operative procedure when a preformed plate is used is not an entirely adequate reason for its universal adoption for cranioplasty. Defects up to 8 cm. in diameter may be repaired at a single and not too lengthy operation with osseous grafts either from the skull, tibia, ilium, or ribs. For repairs of smaller cranial defects, the osteoperiosteal grafts from the outer table of the skull seem to be well suited. The fact that osseous grafts are absorbed in 5 per cent of the cases does not seem to be a serious disadvantage. For the repair of large defects, for which sufficient bone can be obtained only with difficulty, the alloplastic grafts are desirable. The choice of an alloplastic graft is not easy. Only celluloid, which is obviously inferior to the newer plastics and metals, has had the test of time. That all the others will remain inert in the tissue for from forty to fifty years remains to be determined. All of the newer materials—tantalum, vitallium, ticonium, and methacrylate—appear to cause relatively little immediate tissue reactions. The metals and alloys have one distinct disadvantage not possessed by the plastics;

namely, their radiopacity. If roentgenograms of the skull are not required following cranioplasty, this is of no consequence; but if a complication develops, the large mass of radiopaque material is a severe handicap to adequate roentgenographic examination. In cases in which the dura mater has not been penetrated, late sequelae, such as epilepsy, are unlikely; therefore metal plates may be used for repair of the skull defects with little chance of their interference with subsequent roentgenography. However, in those cases in which the dura mater has been penetrated, of which about 40 per cent will probably develop epilepsy, a radiolucent graft such as methacrylate would seem desirable. Although both plastic and tantalum plates appear to modify the electroencephalogram, the alterations do not seem to be sufficient to interfere seriously with the interpretation of the record. Boldrey<sup>7</sup> states that small cranial defects, ranging in size from burr holes to openings approximately two inches, may result in unsightly depressions and may be associated with tenderness. He has used stainless steel wire mesh to repair these small cranial defects. He used 0.0065-inch (40 by 40) and 0.0075-inch (28 by 28) screen in patients. There have been no ill effects. When used to cover frontal burr holes, one layer of screen is placed between the dura and skull before the bone flap is replaced. This remains in position without sutures. Another piece is added outside of the skull, as the double mesh seems to give a better cosmetic result. After eighteen months these patients have demonstrated no untoward reactions.

Robertson and Peacher<sup>8</sup> state that tantalum foil is well adapted for subdural application in the prevention of post-operative sequelae following intracranial surgery. Contrary to previous ex-

perimental results, they have not found dural tantalum foil associated with thickening of dura and arachnoid any more than is seen with ordinary operative procedure exposing the cortex. They report their observations of the effects of tantalum foil when placed immediately over the cortex in six patients. No thickening of the arachnoid was seen. The dura showed minimal thickening. The foil showed no evidence of corrosion. The intervals between the first and second operations were as long as 54 and 110 days. Ingraham and his co-workers<sup>9</sup> summarize their findings on the use of fibrin film as a dural substitute. Fibrin film, prepared from human fibrinogen and thrombin, is cut in a shape corresponding to the dural defect and somewhat larger than it. In a majority of instances it is not necessary to secure the fibrin film in place. A satisfactory result is obtained merely by placing the edges of the fibrin film carefully under the cut edge of the dura. A cuff of the fibrin film may also be affixed to the dura by widely placed silver clips. If sufficient care is used and the film is kept moist, the material is not difficult to suture or to clip, but if it is allowed to dry it is almost impossible to hold the fibrin film in place by any fixation method. After the fibrin film is in place, the wound is closed by the same technic which would have been used had no dural substitute been employed. The authors state that their clinical and experimental studies indicate that it has many advantages over other dural substitutes now available and is apparently a step forward in the prevention of meningeocerebral adhesions.

White and Hamlin<sup>10</sup> report on the uses of tantalum in nerve suture. They report that tantalum wire and sheets are ideal for nerve suture, as they can be drawn to extreme thinness, tie with ease,

and can also be subsequently visualized in the x-ray as a marker of the position of the divided nerve ends. The element causes practically no reaction on the part of neighboring tissue cells. In sheets 0.001 inch thick it can be cut and rolled to fit the ends of a nerve stump from which a painful neuroma has been removed. By crushing the distal open end, a snugly fitting cap is formed which effectively prevents reformation of the neuroma. Annealed rolls of sheet tantalum (0.00075 inch) constitute a distinct improvement over the former use of foil in the protection of nerve anastomosis. Unlike the finer foil, these sheets show no tendency to crumple or fragment and their use is of real value under special circumstances which are often encountered in wartime injuries.

### Spinal Cord Injury

Rogers<sup>11</sup> states that when a paraplegia complicates a vertebral fracture, it is usually a concomitant condition produced at once. However, the onset of paraplegia in such a situation may be delayed. He cites occasions in which there was an interval between the injury to the back and the onset of paraplegia. This interval varied from a matter of minutes to forty-eight hours. In two of the described cases, the paraplegia was transient, resolving completely in a few days' time. In the other two cases, one was persistent and exploration was carried out with improvement in both following the removal of bony encroachment on the spinal canal. He feels that in the transient cases delayed paraplegia, probably due either to subpial hemorrhage or to edema, when fully established at a varying interval after the injury, is sufficient to impair conduction in the cord. Persistent delayed paraplegia is an indication for operation as a rule. Grant<sup>12</sup> reviews his cases of



epidural spinal abscess. In his series of fourteen cases, six were acute, three subacute, and five of the chronic type of abscess. All of the patients were operated on. Of the six patients with acute abscess, two died following laminectomy and four recovered; two with serious neurologic sequelae. Two patients with acute epidural abscess recovered function completely as the result of decompression and drainage. All with subacute abscess survived operation and two had satisfactory restoration of function. Of the five with chronic abscess, one died following operation, and, of the four survivors, but one had complete return of power in the legs with adequate sphincteric control.

The symptoms of an epidural infection appear with almost monotonous regularity. A careful history will show that previous infection has existed, usually a furuncle or other skin infection. Within a week or two the patient has pain, usually very severe, in the back or down the leg. A few days after the pain appears, numbness and finally weakness, progressing on to complete paralysis, develops in the legs and extends upward rather rapidly. Loss of sphincter control may appear early and be complete. Physical examination reveals a sick patient, usually febrile and having leukocytosis. Neurologic studies indicate a cord lesion, more or less complete, depending upon the time at which the patient is seen and the virulence of the infection. Spinal column tenderness may be present corresponding with the upper level of sensory change. Operative intervention at the proper level indicated by the sensory change is urgently indicated. If laminectomy reveals pus, the wound should be packed open if adequate drainage has been assured. **Sulfonamide** derivatives may be used in powdered form in the wound, as well as by mouth.

**Herniated Nucleus Pulposus**—An important aspect of the herniated nucleus pulposus problem requires further investigation; namely, the method of treatment best suited to that type of disc herniation presenting the clinical picture of sciatic syndrome. At present the assumption seems prevalent that the condition requires operation but there is enough evidence to believe that a large majority of cases may recover without operation. Cases recover with *rest* in bed, *heat*, and *drugs* over a period of time not significantly different from that following operation. It seems advisable, therefore, to recommend *operation* only for those cases in which there is intractable pain which cannot be relieved by conservative measures and for cases with recurrences of pain requiring frequent hospitalization with loss of earning capacity. In a significant number of these sciatic syndrome cases, however, it would seem that operation is not necessary; certainly not in the first attack of pain, except under the circumstances mentioned. From a study of the various postoperative results of this condition it is evident that there remains a group of cases in which symptoms remain after operation, just as they do after conservative treatment.

Marble and Bishop<sup>13</sup> attempt to present impartially some of the facts relating to intervertebral disc injury from the standpoint of an industrial surgical clinic. The facts, as gathered, represent a cross section of the work of both neurosurgeons and orthopedic surgeons throughout the country. Of 496 industrial patients suspected of having sustained herniation of the intervertebral disc, 92, or approximately one fifth, were operated upon; while four fifths received other therapy. Less than 50 per cent of the cases operated on showed a favorable end result. Return to former occupation within six

months after operation was possible in 34 cases. Return to work was possible within one year in 9 cases. In 49 cases the disability lasted more than one year. Their studies agreed with the report of Mixter in that the vast majority of failures occurred in cases that had had spinal fusion performed. Poppen<sup>14</sup> studied 400 surgically proved cases of ruptured intervertebral disc in one or more spaces in which eighteen months to ten years had elapsed since surgical intervention. The series represents 8 per cent of the patients who entered the Lahey Clinic with the complaint of low back pain. He emphasizes again that even though the herniated disc is an important cause of low back pain and sciatica it is by no means a predominant one. The most constant objective finding was a positive straight leg reaction, which was present in 90 per cent of the patients when the protrusion was in the third, fourth, or fifth lumbar segment. Seventy-five per cent of the patients demonstrated spasm of the low back muscle; 48 per cent had sensory changes in the fifth lumbar or first sacral dermatomes or both. Narrowing of the disc space was not an assurance that a posterior dislocation of disc was present. He recommends the conservative measures of treatment be utilized in the mild cases and feels that surgical intervention is only indicated in those patients who have repeated disabling attacks of sciatica and who are unable to work from time to time because of their symptoms. Patients with predominating leg pain and with minor back difficulty whose roentgenograms show no bone changes should have only the disc removed, whereas for a patient who has predominating back pain, with abnormal facets and evidence of an unstable back and who has to do hard manual labor, removal of the degenerated cartilage with fusion is indicated.

The relief of sciatica was satisfactory in most of the operated cases. Residual back discomfort on heavy lifting or sitting in a cramped position occurred in almost one half of the cases. This percentage was not materially altered in those who also had fusions. Fifteen per cent of the patients operated upon did not obtain relief. Voris<sup>15</sup> describes the selection of patients for operation with this condition. He states that conservative treatment is indicated in patients with mild symptoms who do not have to perform physical labor or strenuous exercise. Another group of patients with disc protrusion that is notoriously likely to obtain poor results with surgery consists of the compensation cases. Patients in this group with low pain thresholds, inadequate personalities, or who indicate resentment against their employer or the insurance carrier will seldom obtain a good result, at least during the period of compensation. It is his opinion that the combined operation (spinal fusion combined with the removal of the disc protrusion) should be considered (1) in cases of multiple or recurrent disc protrusion; (2) where there is roentgenographic, clinical, or surgical evidence of instability of the lumbosacral spine; (3) where low back pain is severe and disabling for a long period before the onset of sciatic radiation; and (4) where the patient's occupation is one of heavy labor or demands a great deal of lifting.

Munro<sup>16</sup> believes that a clinical diagnosis of a posterior herniation of the nucleus pulposus of a ruptured lumbar intervertebral disc which is based only on the history and physical examinations, if unconfirmed by other objective signs, is at best only a "possible" diagnosis. Surgery is not justified under such circumstances. If one can demonstrate a sensory deficit that corresponds

to the peripheral distribution of a low lumbar or upper sacral root, together with atrophy and loss of ankle jerk in the same leg, a diagnosis of irritation or compression of this particular root is justified. A positive straight leg raising or Laseque test, limitation of low back motion, a change in the lumbar curve, spasm of the erector spinae muscles, and local tenderness in the lumbosacral area indicate only that the patient has some trouble with the lower part of his back, lumbosacral roots, or cauda equina, and neither confirms nor denies the diagnosis of a herniation. He concludes that very often the level of herniation is usually not determinable on the basis of pure clinical data. Multiple herniations cannot be diagnosed without preoperative visualization of the lower subarachnoid space. Certain diagnosis, both concerning the presence of a herniation or herniations and concerning the level, depends on adequate visualization of the lumbosacral subarachnoid space by some opaque contrast medium. Childe<sup>17</sup> discusses the rôle of x-rays in the diagnosis of posterior herniation of the intervertebral disc. He stresses that plain x-ray films always be made first. These films usually are not diagnostic of such herniation but may offer suggestive evidence and may help to exclude other lesions. Myelography, when properly performed using pantopaque with subsequent aspiration, is an accurate and safe measure. Multiple disc herniations are not uncommon and many unsatisfactory results may be explained on this basis if operation is undertaken without previous myelography. Herniation of sufficient size to produce great disability may cause only comparatively small deformities of the subarachnoid space. Hence the use of a relatively large quantity of oil is advisable, and multiple spot films should be made routinely to avoid miss-

ing minor deformities not readily seen under the fluoroscope. He has found that herniated discs in the cervical region are often complicated by hypertrophic bone formation. Myelography will also differentiate between a tumor and herniated disc. Ver Bruggen<sup>18</sup> reports nine cases who suffered from acute compression of the cauda equina by large extrusions of the nucleus pulposus of the intervertebral discs. In all of these cases the lesion was in the region of the lower lumbar vertebrae. The symptom complex was of variable degree of intensity from slight weakness of the legs below the knee, with saddle hypesthesia, to severe sphincter disturbances. In most cases there was a "cogwheel" history, in that the picture developed in successive acute short episodes. Intermittent symptoms were characteristic as was the history of gradually progressive spurts of trouble. Few of these patients were operated upon and one died before anything could be done. The location of the extrusion was in the lumbosacral joint in three cases, between the fourth and fifth lumbar vertebrae in three cases, and between the third and fourth lumbar vertebrae in two cases. He emphasizes that in these cases with acute compression of the cauda equina area early diagnosis and operation are essential. He found that even when these two criteria are met, recovery may be slow and incomplete. Elliott and Kremer<sup>19</sup> report on a brachial pain syndrome which is secondary to herniation of cervical intervertebral disc. The authors give the histories of eight patients with brachial pain. There was a uniform distribution of pain in the posterior aspect of the shoulder and upper arm and the radial border of the forearm and sometimes in the upper pectoral region. There were paresthesias in the thumb, index, and middle fingers. In some cases there was

a history of acute stiff neck. The signs included limitation of movement of the neck; pain produced in the arm by movements in the neck and by downward pressure on the head; and tenderness, weakness and wasting of the upper fibers of the pectoralis major, triceps, and extensors of the wrist and fingers. The triceps jerk was reduced or absent and there was usually hypalgesia of the thumb and index finger. Contrast myelography in three cases showed a filling defect opposite the sixth intervertebral disc involving the seventh cervical root on the afflicted side. From a review of the literature, Browder and Watson<sup>20</sup> collected sixty-nine verified cases with protrusion or herniation of a part of the cervical disc. In this paper they present their experiences with twenty-two cases in which this lesion had disturbed the function of the cervical spinal cord with or without the cervical nerve roots. Twenty-one were verified at operation and one at necropsy. They emphasize that a negative Queckenstedt test does not exclude the presence of such a lesion.

### Cranial Trauma

**Acute Craniocerebral Trauma**—Summarizing his observations on 100 cases of compound comminuted fracture of the skull, Campbell<sup>21</sup> says that inner table fractures were sometimes overlooked and occasionally led to serious complications. Tripod incisions often give trouble; it is recommended that they be avoided when possible. Convulsions were not common in the first few weeks; their occurrence was sometimes the early manifestation of abscess formation. Superficial wound infections of varying degrees developed in 19 cases, while in 22 the infections were deep seated. These were manifested by abscess, meningitis, or cerebral fungus. Incomplete débridement was the largest single factor contribut-

ing to wound infection. In those cases in which all bone fragments had been removed infection was not common and seldom deep, whereas if débridement had been incomplete or not performed, infection was common and usually deep. Treatment consisted in these cases of *evacuation of pus* and *removal of associated bone fragments and foreign bodies* as well as adjacent necrotic tissue and old blood. Abscess capsules were disturbed as little as possible. *Sulfonamide therapy* was employed as an adjuvant.

Glaser and Shafer<sup>22</sup> report their experiences in 111 cases of depressed fracture of the skull in a series of 1500 cases of head injury under observation over a period of time varying from one to fourteen years. They conclude from their series of cases that the following principles should be carried out in the treatment of depressed skull fracture: (1) Avoid elevation of simple and compound rounded, nonspiculated depressions confined to silent areas of the brain. (2) Avoid elevation of simple and compound fractures, if not over the motor area, in which a large segment of bone is separated but hinged at one side, and in which, as is usual in fractures of this type, the depth of the depression is not great. (3) Elevate simple and compound rounded depressions over the motor area. (4) Elevate the fragment in all cases of spiculated fractures. (5) Elevate in all cases where uncertainty exists as to whether spiculation is present. The force of the blow struck, and not the existence of a simple rounded depressed area of bone, is responsible for the underlying brain damage. In those cases wherein extensive brain damage has occurred, early elevation will not prevent sequelae. In this series of 111 cases, complete recovery occurred in 45 patients (40.5 per cent); partial per-

manent disability in 30 patients (27.0 per cent); total permanent disability in 22 patients (19.8 per cent); fatality in 14 cases (12.6 per cent). If the patient does not return to work within four months, the probability of some type of permanent disability is very great. Approximately 85 per cent of those with momentary or no unconsciousness recovered without disability. Meller,<sup>23</sup> in his study of 1280 cases of brain trauma necropsied at the University of Minnesota, reports the following facts concerning his study: In general, the location of the skull fracture has very little effect upon the nature of brain pathology resulting. Cerebral lacerations are somewhat more common with the combined base and vertex involvement than with other fracture locations. The age of the patient does not influence the type of brain lesion resulting from the trauma. The type of brain injury has relatively little correlation with the survival time of the patient. Occasionally, cases of intraventricular hemorrhage will show relatively long survival time.

### Closed Head Injury

**Cerebral Hematoma**—The origin of excessive subdural fluid accumulations have been designated by some as subdural hygroma. Wycis<sup>24</sup> reviews the literature on subdural hygromas. As regards symptomatology in these cases, a history of injury (direct or blast) is usually available. There follows a period of unconsciousness which may vary from minutes to weeks. The cases associated with blast concussion may show only an initial state of "daze" which may progress to confusion. Headache is the most frequent symptom. Dizziness is another frequent complaint. Other symptoms may vary from nervousness and irritability, confusion, aphasia, or hemiplegia to

semicoma and stupor. Occasionally one may see the classical triad of headache, vomiting, and papilledema, thus mimicking the brain tumor. The author suggests that bilateral trephination of the skull is the surgical procedure of choice. Rowbotham and Ogilvie<sup>25</sup> report two cases of chronic cerebral hematoma which were operated upon. Recovery followed and both patients regained health. They feel that the operation is a successful venture in the therapy of cerebral hemorrhage, especially when the hemorrhage is secondary to a rupture of a congenital aneurysm. They chose to operate at the stage of chronic subdural hematoma and not at the stage of acute cerebral hemorrhage. They state that in those cases of hemiplegia following subarachnoid hemorrhage it is also wise to operate even when there is no secondary rise in intracranial pressure. The authors caution that surgery has little to offer in ordinary apoplexy, or, in fact, in the early stages of cerebral hemorrhage due to any cause. Hamby<sup>26</sup> points out that while the more common types of intracranial hemorrhage are well known, spontaneous, limited, removable intracerebral hematomas are less familiar. He reports sixteen cases of gross intracerebral hematomas that were drained. There were fourteen recoveries and two deaths. Cases due to cranial injury or skull fracture were not included in his series. Seven of the cases were associated with cerebral arterial disease. One case was proven and three were suspected to be due to ruptured aneurysms of the major blood vessels. One case was of delayed posttraumatic intracerebral hemorrhage. Kennedy<sup>27</sup> presents the following classification of his conception of the clinical entities which should be included under the heading of closed head injuries:

1. Concussion with impairment or loss of consciousness lasting from several seconds to a few minutes.
2. Contusion:
  - (a) simple or minor with or without loss of consciousness
  - (b) moderate, mostly with loss of consciousness
  - (c) severe, with loss of consciousness
    - (1) localized with bruise or laceration
    - (2) generalized with lacerations or intracranial hemorrhages with signs of increased intracranial pressure (ocular, lumbar pressure, edema)
    - (3) acute cerebral shock.
3. Hemorrhagic effusions (including organized hematomas and hygroma):
  - (a) intracerebral
  - (b) epi- (or extra-) dural
  - (c) subdural:
    - (1) acute
    - (2) chronic

He reviews in a comprehensive fashion the entire field covered by this classification. Denny-Brown<sup>28</sup> reviews the disability arising from closed head injury based on a series of 200 cases. Few of the injuries were of great severity, consisting chiefly of various degrees of scalp injuries and loss of consciousness. Twenty-seven patients had post-traumatic amnesia lasting over twelve hours, twenty-two over two days, eight over seven days. Eighteen cases had clear evidence of fracture of the skull. A total of 110 patients (55 per cent) complained of symptoms in convalescence. The symptoms were directly referable to structural physical disorders in 16 patients, to headache in 81, dizziness in 46, and mental symptoms in 70.

These symptoms were frequently associated, but each could occur alone. The association of headache, dizziness, and psychiatric symptoms ("postconcussion syndrome") occurred in thirty patients. Absence from full occupation occurred in 40 patients by reason of other injuries or unrelated causes. In the remaining 170 patients, 42 returned within one week after injury, 71 within one month, 23 in the second month, 20 between the third and fifth months, 9 between six and nine months, and 5 nine months or more after injury. Such disability had variable relationship to the various posttraumatic symptoms. Psychiatric symptoms had the highest correlation with prolonged disability. Factors of bad prognostic significance in relation to return to occupation within two months of the injury, and within six months of the injury, were analyzed. In each case, features indicative of severity of injury (prolonged disorientation, abnormal neurologic signs, blood in the spinal fluid, electroencephalographic abnormality) and those indicative of psychologic stress (initial excitement or apathy, occupational worries, anxiety over compensation) were intermingled. The symptoms associated with prolonged disability were predominantly mental symptoms related to anxiety. Even after severe injuries, cranial nerve paralysis, dizziness and headache, and personality change accounted for a minor part of the disability. Intellectual disorder played no significant part. The environmental factors of the injury were in total effect more important in accounting for disability than were the factors indicative of severity of injury. Neither can be neglected in the assessment of prognosis. The extensive association between head injury and psychiatric factors indicates possibilities for lessening disability by psychiatric treatment. Adler,<sup>29</sup> in a sta-

tistical analysis of 200 cases, studied the mental symptoms following head injury. She found that posttraumatic mental symptoms developed in 31.5 per cent of these cases. Of the patients with posttraumatic mental symptoms, the largest group, 48 patients, had posttraumatic anxiety states. In all but one of these 48 patients, the issue was complicated by environmental difficulties such as occupation, litigation, and other factors. Mental symptoms, particularly symptoms of anxiety, are, with headaches and dizziness, the commonest symptoms in convalescence. They are also the most common symptoms relating to disability and are undoubtedly the major cause of disability in particularly prolonged disability. Ecker and Anthony<sup>30</sup> describe the basis for a few ophthalmic syndromes associated with closed head injuries. They show that the fixed dilated pupil of Hutchinson is an infallible sign of raised intracranial pressure. It is usually due to a laterally placed intracranial lesion of the same side, which most often is in the temporal but may be in the frontal or parietal lobe. The pupillary change is caused by herniation of the medial part of the temporal lobe into the tentorial notch, the so-called tentorial pressure cone. This herniated portion of temporal lobe is said to pinch the ipsilateral oculomotor nerve but is more likely to act by displacing and rotating the midbrain in such a way as to exert traction on the nerve. Bilaterally dilated fixed pupils soon after a head injury indicate a bad but not hopeless prognosis. If they are associated with neurogenic hyperthermia, rapid pulse, and quickly rising rectal temperature, with a cold skin and decerebrate rigidity, there is damage to the midbrain. The prompt intravenous administration of plasma and deliberate cooling of the skin may result in dramatic improve-

ment. Argyll-Robertson pupils may result from head injury. The lesion in these cases may be either in the central nervous system itself or in the peripheral efferent pathway to the pupil.

### Nerve Injuries

The repair of nerve injuries continues to be an important problem for neurosurgical investigation. Spurling<sup>31</sup> and his associates report failure with the use of whole, fresh, homogenous nerve grafts in man. There was no clinical evidence of nerve regeneration after an appropriate time interval had elapsed following transplantation of the neural tissue. One of the main points of difference between successful animal homografts and human failure may lie in the girth of the engrafted tissue. Singer<sup>32</sup> describes a method of uniting nerve stumps without the use of thread sutures. The technic, designated as the fibrin adhesive method, involves the use of a thin smooth film of fibrin prepared from products of fractionation of human blood plasma. The film is impregnated with thrombin, surfaced with fibrinogen and then applied to the opposed nerve stumps by one of several methods. The fibrinogen as it clots binds the film to the surface of the nerve and then serves to transmit the stress of retraction of the stumps to the film. In addition to maintaining apposition of the stumps, the film serves as an envelope enclosing the nerve stumps and nerve wound in a continuous channel. The fibrin adhesive method of nerve splicing has the advantages of simplicity of application and of introducing no extraneous materials or obstacles to growth into the nerve trunks themselves or between the stumps. The film is transparent and consequently allows for continued observation of the nerve stumps throughout the operation. Spurling<sup>33</sup> reviews the management of

peripheral nerve injuries in the European theater of operations. He pays particular attention in this study to the question of early nerve surgery. The essential factors of the program employed were: (1) Débridement and delayed primary closure of the wound, with approximation or anchoring of the severed nerve ends if they were visualized at the first operation; (2) suture of the divided nerve within twenty-one to ninety days after wounding, but preferably between twenty-one and twenty-eight days, when the least technical difficulties and the best end results can be expected; (3) a judicious use of immobilization during transportation and after neurorrhaphy, preferably by removable splints; (4) preoperative and postoperative physical therapy. In many of the simpler cases in this series operations were performed under local procaine infiltration analgesia. Operations on the sciatic nerve were usually performed under spinal analgesia. All brachial plexus injuries and many combined injuries of the upper arm were handled under intratracheal ether anesthesia. Every surgeon who participated in the peripheral nerve injury program was instructed in the following generally accepted technical principles of nerve repair: (1) That the nerve ends must be accurately trimmed until essentially normal tubules were visible; (2) that the divided ends must be approximated with the greatest care by interrupted epineural sutures; (3) that the suture line must be perfectly free from tension; (4) that hemostasis must be rigid. The use of a through-and-through suture (sling suture) was optional. The suture material recommended was fine tantalum wire swedged on an atraumatic needle. A small cuff about the suture line was used in almost all the cases handled in the European theater of operations.

Usually it was of rolled tantalum foil. Casts for the correction of deformities due to nerve injuries were prohibited, removable splints being preferred. Physical therapy utilized was daily galvanic stimulation for the denervated muscles beginning with fifteen brisk contractions daily and progressing gradually to thirty contractions. Other measures include massage, active and passive motion, and the use of dry and moist heat as indicated. Norcross<sup>34</sup> reports on the use of *penicillin therapy* in the early repair of neural wounds. He concludes that with prophylactic or suppressive penicillin therapy, surgical treatment can be carried out for neural wounds in the face of infection much earlier than has heretofore been deemed advisable. He reports twelve such cases. All wounds healed by first intention without complication. To patients with infected wounds, penicillin was given for four days before and for ten or more days after operation in doses of 20,000 units every three hours. Local instillation of penicillin solution was used in two cases, while in most of the others the wound was dusted with *sulfanilamide* before closure. Gurdjian and Smathers<sup>35</sup> report their experiences in the treatment of peripheral nerve injuries after fractures. The fifty-three nerve injuries for which they performed operations included thirty-two radial, nine ulnar, three median, eight peroneal, and one sciatic nerve. Early exploration in cases of nerve lesions associated with fracture of long bones is justifiable after complete study of the history, physical findings, and x-ray films. If, from an orthopedic standpoint, open reduction is the procedure of choice, the involved nerve can be explored at the same time. Early exploration in ulnar nerve palsy associated with fracture of the medial condyle of the humerus is preferable. Anterior



transposition of the nerve may then be carried out. Early exploration of primary peroneal palsy is desirable in injuries of the knee joint with fracture of the upper end of the fibula. In fractures of the middle third of the humerus complicated by radial palsy, exploration in eight to ten weeks is justifiable if there are no evidences of returning function. In compound fractures associated with nerve lesions early repair is feasible, particularly with present-day chemotherapeutic measures. A nerve should be explored if there is no evidence of regeneration three to four months after a fracture of the neighboring bone.

It has been shown by Richter and his associates that measurement of the electrical resistance of the skin provides an accurate and objective means of diagnosis in peripheral nerve injuries. Areas of high resistance may be mapped out by a small exploratory electrode held in the hand with the reference electrode attached to the ear lobe that has been punctured with a pin prick to eliminate its skin resistance. These areas of high resistance represent skin that has lost its sympathetic nerve supply. They can be outlined with a high degree of accuracy and usually correspond closely to the area accurately mapped as analgesic or anesthetic, and may be related only to an area of hypesthesia. The high skin resistance is due principally to the inactivity of the sweat glands in a denervated area. The instrument devised for this test has been called a dermohmmeter. Jasper<sup>36</sup> has made certain changes in the original instrument which he considers to be an improvement in the dermohmmeter's clinical use. Jasper and Robb<sup>37</sup> report on their studies of electrical skin resistance in peripheral nerve lesions with the use of the dermohmmeter. They conclude that denervated skin shows a marked increase of elec-

trical resistance a few minutes following nerve section and remains at a relatively high level until neurotization takes place. It can be demonstrated more clearly when the sweat glands of surrounding areas are active. They are of the opinion that Richter's skin resistance method is an objective, practical, and precise test for the diagnosis of peripheral nerve injuries involving the sympathetic supply to the skin. The new dermohmmeter has made possible the testing of more patients without artificial diaphoresis.

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## ORTHOPEDIC SURGERY

JOHN ROYAL MOORE, M.D.

### Penicillin Therapy in Acute Osteomyelitis

Thirty-four cases of acute osteomyelitis were treated with penicillin. Solutions of sodium salt of penicillin, in sterile physiological saline with a concentration of 5000 units per cc. were used in all but one case. The solution was administered by continuous intravenous drip and interrupted intravenous and intramuscular injection. The diagnosis was made early and the penicillin treatment was instituted apparently without surgical drainage. Both general and local infections were brought under control so thoroughly that a minimal amount of bony damage resulted. Moderate delay in diagnosis and treatment increased the extent of bony damage but the infection was nevertheless quickly arrested with the aid of drainage and without sequestration. Small localized abscesses were treated by aspiration and followed by an injection of solution of penicillin. Prompt surgical drainage was required in large abscesses. After the onset of penicillin therapy, a period of thirty-six or more hours usually occurred before the beginning of clinical improvement, even in the early cases. Occasionally cases of acute osteomyelitis were seen

which were so fulminating that they would not survive the forty-eight hours or more necessary for the full effect of the penicillin. These were subjected promptly to the surgical procedure indicated.

Penicillin is a powerful antibiotic agent in the treatment of acute osteomyelitis. Fig. 1 illustrates the radiologic changes noted at the beginning and the end of the osteomyelitic attack following the penicillin therapy (comparatively mild case). Fig. 2 shows repeated radiographs chronologically arranged and demonstrates the rather remarkable recovery of a case of osteomyelitis of the humerus, given penicillin therapy. Fig. 3 consists of two photographs illustrating the marked change in the clinical picture before and after penicillin therapy.<sup>1</sup>

### Treatment of Spondylolisthesis

Dandy,<sup>2</sup> in searching for a simple and effective means of producing spine fusion in spondylolisthesis, experimented with the removal of the intervertebral disk between the affected vertebrae, hoping to get an intervertebral fusion. His observations from a series of patients upon whom this operation was performed led to "unexpected conclu-



November 18,  
1943

December 1,  
1943

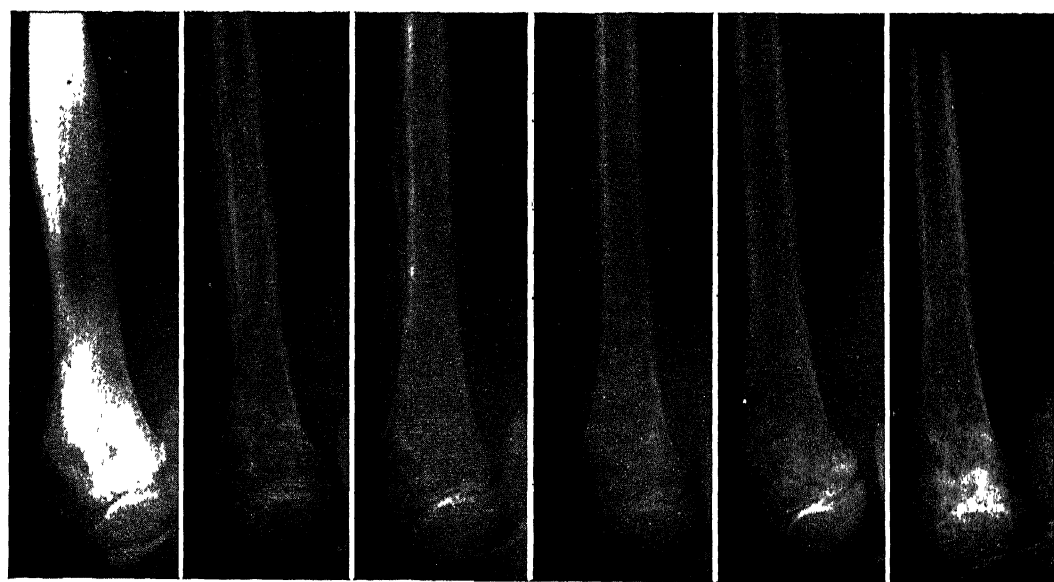
December 13,  
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May 5,  
1944

August 25,  
1944

Fig. 1—M T. Case 5. (Altemeier, W. A. and Helmsworth, J. A.:  
Surg., Gynec. & Obst. 81: 138 (Aug.) 1945.)



March 31,  
1944

April 8,  
1944

April 12,  
1944

April 18,  
1944

April 27,  
1944

June 22,  
1944

Fig. 2—R. S. Case 21. (Altemeier, W. A. and Helmsworth, J. A.:  
Surg., Gynec. & Obst. 81: 138 (Aug.) 1945.)

sions." First of all, the spondylolisthesis is usually responsible for only a part and at times none of the symptoms; secondly, in most instances, it is not the spondylolisthesis or even the disk that is at the site of the spondylolisthesis that causes the symptoms, but rather another disk or disks above or below the area; thirdly, that the cure usually depends upon the removal of the other disks or disk than

### Spontaneous Bilateral Fracture of the Neck of the Femur Following Irradiation

Baensch in 1927, Ewing in 1926, Baker and Hight in 1941, and others have reported cases of irradiation fracture. Heyman<sup>3</sup> presents a rather typical case of spontaneous fracture of the neck of the femur (bilateral) following prolonged irradiation. A fracture of one hip



Fig. 3—R. P. Case 27. Diagnosis: Acute hematogenous osteomyelitis of left humerus. The appearance of the patient at the start of penicillin therapy and two weeks later. (Altemeier, W. A. and Helmsworth, J. A.: *Surg., Gynec. & Obst.* 81:138 (Aug.) 1945.)

the one at the site of the spondylolisthesis. This, too, must be extirpated.

Unless Dandy's article is read very carefully one is apt to conclude that he is ignoring the congenital defect in the bony neural arch. He does not, but emphasizes an extremely important fact, namely, that pain in spondylolisthesis may be caused, in fact, usually is caused, by intervertebral disk derangements rather than the congenital defect in the inferior articulating (zygapophysial) process.

occurred fourteen months after completion of irradiation and the other hip at eighteen months. Pain was present in each hip at least four weeks before the roentgenographic changes were demonstrable. The author calls attention to the similarity between the irradiation fracture and the March insufficiency or so-called exhaustion fracture observed so frequently during World War II. Internal fixation with the Smith-Petersen nail has apparently brought about solid union at the fracture sites. Subsequent

arthritic changes due to irradiation must be looked for.

The importance of this presentation lies in the fact that irradiation fractures are probably going to increase in num-

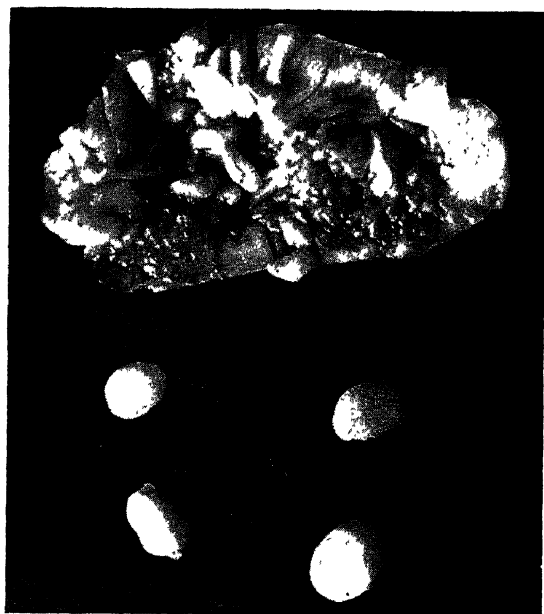


Fig. 4—An area of disintegrating cartilage excised from the articular surface of the patella, and four smooth rounded cartilaginous loose bodies which had become detached from the degenerated area and were removed from the knee joint at the time of operation. They contained no calcium and therefore were not demonstrable by roentgenogram. (Case 1.) (Cave, E. F., Rowe, C. R. and Yee, L. B. K.: *Surg., Gynec. & Obst.* 81: 446 (Oct.) 1945.)

ber with the more extensive use of irradiation therapy. Even though the more important bones and joints may be walled off, spontaneous fractures might easily occur in such bones as the pelvis, spine, etc. The response to internal fixation should be emphasized. Apparently these fractures heal, provided they are given the same consideration as ordinary fracture. To this irradiation complication may be added another and very important one, namely, irradiation sarcoma. (See article by Hatcher<sup>17</sup> included in this review, p. 792.)

### Chondromalacia of the Patella

The purpose of the paper is to call attention to what the author<sup>4</sup> believes to be a common cause of internal derangement of the knee in adolescents and young adults. Chondromalacia of the patella may be suspected by local tenderness under the patella elicited by sliding the patella from side to side, by percussion on the patella or pressing on it vigorously. (See Fouche's sign described by duToit and Enslin in the present review under the title "Analysis of One Hundred Consecutive Arthroto-



Fig. 5—Knee joint opened through a median parapatellar incision. Articular surface of patella turned upward, demonstrating extensive area of chondromalacia in the central portion. There was thinning of the cartilage over the inner aspect of the medial femoral condyle. The synovia was markedly thickened and congested. Roentgenograms were entirely normal. (Cave, E. F., Rowe, C. R. and Yee, L. B. K.: *Surg., Gynec. & Obst.* 81: 446 (Oct.) 1945.)

mies for Traumatic Internal Derangement of the Knee Joint.") Eleven cases were reported. The patients were returned to full military duty, three to

limited service duty. Two of the cases were returned to the United States because of chronic synovitis of the knee. Treatment consisted of either a patella-plasty—horizontal resection of the dorsal two thirds of the patella with interposition of a flat of fat between the remaining patella and the condyles, or complete removal of the patella. Figs. 4 and 5 are illustrative of the pathology encountered at the time of the operation.

tension needed to push home the piston). A collodion dressing is applied and a crepe bandage is used to compress the suprapatellar pouch and increase the amount of air in the joint. With the patient lying on his side, the line of the knee joint is marked under the fluoroscope in order to make sure that the beam (x-ray) passes exactly along the joint line. The articular surfaces are separated on the side of the suspected



Fig. 6.



Fig. 7.

Fig. 6—Left, low power: Section of cartilage from area of chondromalacia. Note the proliferation of cartilage cells, particularly at the surface, and the disruption of the usual architecture. (Case 1.) (Cave, E. F., Rowe, C. R. and Yee, L. B. K.: *Surg., Gynec. & Obst.* 81: 446 (Oct.) 1945.)

Fig. 7—Right, high power: The same field showing the pyknotic hyperplastic cartilage cells. (Case 1.) (Cave, E. F., Rowe, C. R. and Yee, L. B. K.: *Surg., Gynec. & Obst.* 81: 446 (Oct.) 1945.)

### Air Arthrography in the Diagnosis of Torn Semilunar Cartilage

Herzog<sup>5</sup> advocates air arthrography in the study of internal derangement of the knee. The method is as follows: "A No. 20 needle is inserted in the prepatellar pouch after the injection of a little novocaine. Any effusion should be aspirated. Air, filtered through several layers of gauze, is injected with a 20-cc. syringe fitted with a three-way tap. The quantities used vary between 60 and 20 cc. (it is best to be guided by the distention produced and the amount of

cartilage by abducting or adducting the tibia on the femur, employing a sandbag as a fulcrum. For instance, if the internal meniscus is suspected, the tibia is adducted on the femur and if the external meniscus is suspected it is abducted. With the tube horizontal and the central beam passing through the knee tangentially, three views (Fig. 8) are taken of the suspected cartilage. If other joint lesions are suspected, the usual three views of the whole knee joint is taken, AP, lateral and intercondylar. Films showing the retropatellar space will dis-

close chondromalacia patellae if they are present.

Air arthrography was employed in twelve cases. Eight of these cases had torn internal menisci. Four cases were normal. Operation or subsequent history confirmed the above findings.

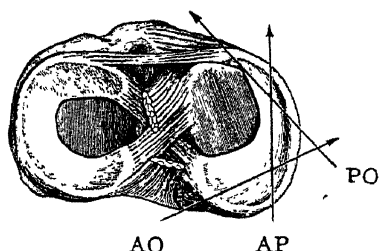


Fig. 8—Showing the direction of the radiograms taken through the knee joint. *AP* = anteroposterior view, *PO* = posterior oblique, *AO* = anterior oblique. (Herzog, E. G.: *Lancet* 2: 5 (July 7) 1945.)

Air arthrography has had its high and low peaks in the diagnostic armamentarium. The high percentage of success in Herzog's group plus the very wide usage of air in myelography should revive its usage.

### Sagittal Cleft (Butterfly) Vertebra

The authors<sup>6</sup> call attention to a congenital division of the vertebra (vertical split separating the bodies into two lateral halves) first described by von Rokitsansky in 1844 (quoted from Fischer and Vandemark). Fig. 9 is illustrative of the variations in the sagittal cleft. Two cases were encountered in the service, one a so-called butterfly third lumbar vertebra and the second a butterfly second thoracic vertebra (Figs. 10*A*, 10*B*, 10*C*, 10*D*).

The authors' very efficient summary brings out very important facts pertaining to this anomaly.

"The reported cases of sagittal cleft vertebra are too few to permit a final clinical evaluation of the condition. It is evident, however, that from an ortho-

pedic standpoint, the cases fall into two principal groups, the symptomatic and the asymptomatic. The symptomatic group is usually characterized clinically by the presence of mild, moderate, or severe local deformity occasionally followed by pain, and roentgenographically by anterior compression of the vertebral body halves, and less frequently by inequality of the two vertebral halves or their lateral displacement. In these cases, the sagittal cleft roentgenographically distinguishes the anomaly from unreduced vertebral body fractures with anterior or lateral compres-

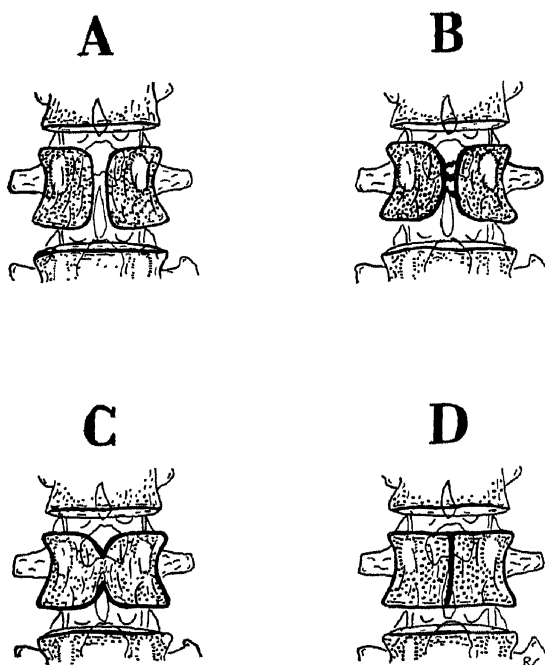


Fig. 9—Variations in the sagittal cleft which may be: *A*, Wide; *B*, bridged by small bony strands; *C*, crossed by a bony bridge; or *D*, narrow. Further variations in the butterfly appearance result from inequality of the vertebral halves or their lateral displacement. (Fischer, F. J. and Vandemark, R. E.: *J. Bone & Joint Surg.* 27: 695 (Oct.) 1945.)

sion and lateral displacement. Clinically, the symptomatology may resemble that seen in old unreduced fractures of the vertebral body. Certain asymptomatic cases are characterized clinically by the absence of deformity. Roentgenograph-

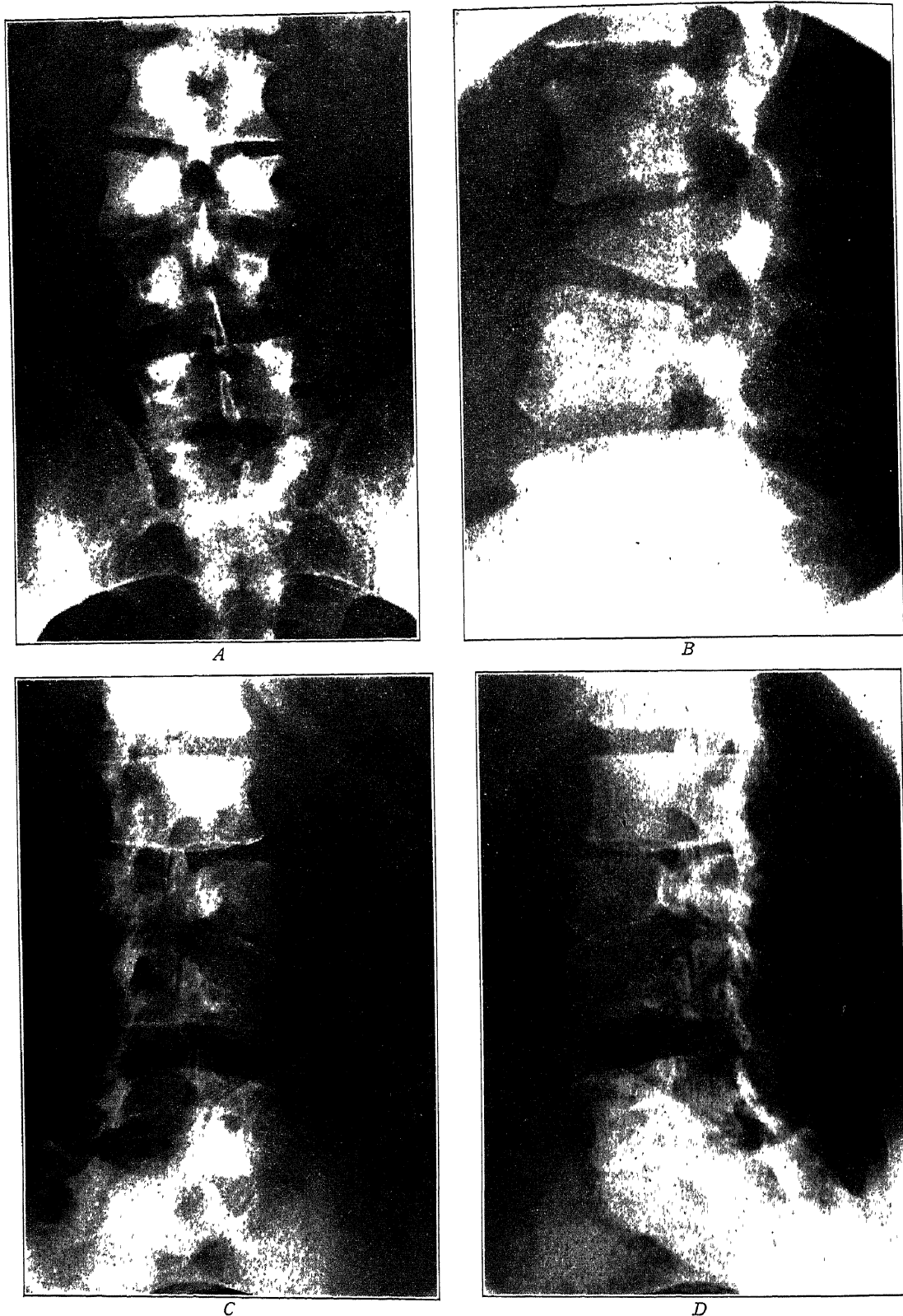


Fig. 10—*A*, Roentgenogram showing the body of the third lumbar vertebra divided into two unequal halves. *B*, Lateral view. The wedging anteriorly of the third lumbar vertebra simulates a compression fracture. *C*, Right oblique view. *D*, Left oblique view. (Fischer, F. J. and Vandemark, R. E.: *J. Bone & Joint Surg.* 27: 695 (Oct.) 1945.)



ically, they show division, not always complete, of the vertebral body into two equal halves without anterior compression or lateral displacement. It seems unnecessary to discuss in detail the embryological and pathological aspects of this anomaly, which have been thoroughly reviewed so recently by Ehrenhaft (1943)."

### Retardation of Bone Growth by a Wire Loop

The author<sup>7</sup> has offered a method by which a wire loop was passed around the epiphyseal cartilaginous plate in the frontal plane (see Figs. 11A and 11B). Very definite arrest in growth occurred.

The value of this contribution consists primarily in the fact that a temporary



Fig. 11-A—Case 1. E. G. July 30, 1942. Anteroposterior view showing the wire as placed at the time of operation (March 27, 1942). (Haas, S. L.: J. Bone & Joint Surg. 27: 30 (Jan.) 1945.)



Fig. 11-B—July 30, 1942. Lateral view. (Haas, S. L.: J. Bone & Joint Surg. 27: 30 (Jan.) 1945.)

arrest of a rapidly growing bone could well be employed in the equalization of leg length in such bones as tibia, fibula, radius, and ulna. Phenister in 1933 proposed an epiphysiodesis for the equalization of leg length. This method consisted essentially of obliterating the epiphyseal plate or plates of the more rapidly growing side. The method has been very useful. Its principal drawback is the fact that accurate equalization is impossible. The good leg may be shortened too much or not enough. Asymmetrical arrest may lead to bow leg, knock-knee, recurvatum and comparable deformities in the upper extremities. The procedure suggested by Haas is of value in that a temporary arrest may be employed until the extremities are equal and then the growth again liberated. The

growth rate by this method would appear to be controllable. The number of cases are too few to justify a true evaluation at this time.

### The Intervertebral Disk: Its Microscopic Anatomy and Pathology

The authors<sup>8</sup> present a most valuable contribution concerning the pathologi-

13A, 13B, 14, 15, 16, 17A, 17B, 18, and 19 are illustrative.)

The summary given by the authors is excellent and is quoted *in toto*:

"The pathological changes studied in this series include hypertrophic arthritis, nuclear expansions, ballooned disks, thinned disks, nuclear herniations in the vertebrae (Schmorl bodies), anterior and posterior nuclear protrusions, calcification of the nucleus pulposus, in-

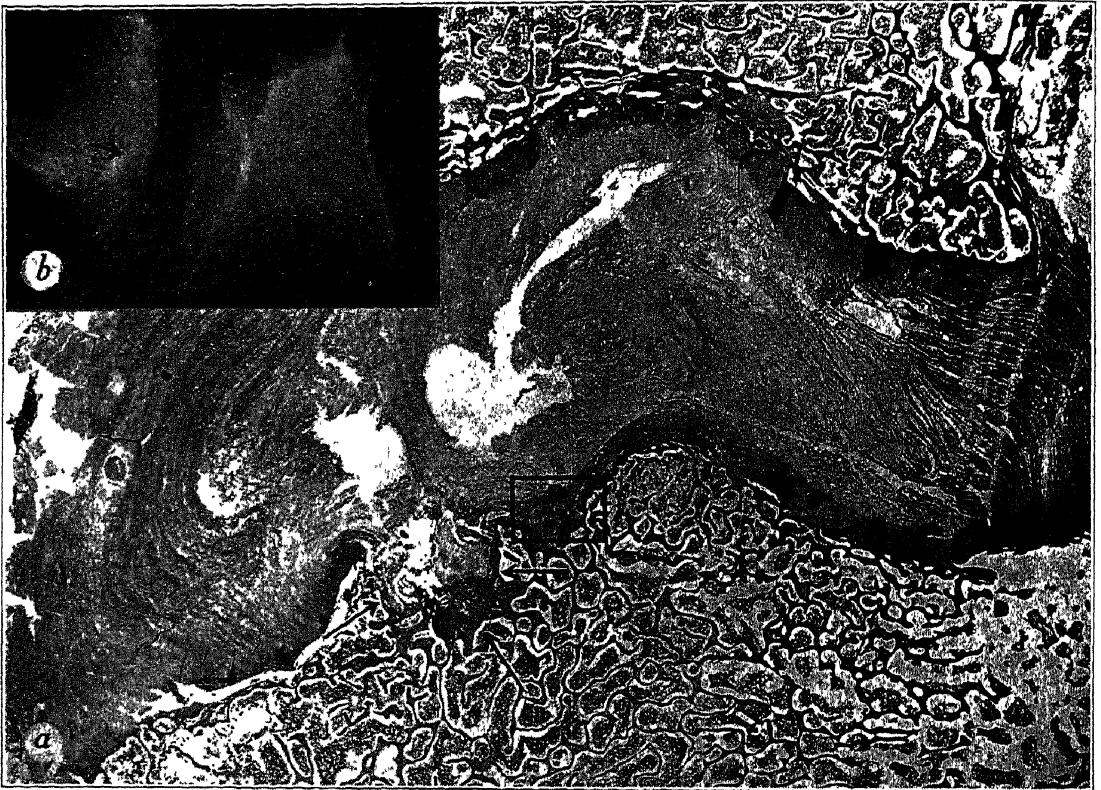


Fig. 12—Intervertebral disk of a youth, aged twenty years. *a*, Section ( $\times 3.75$ ) showing nuclear expansion. Arrows indicate a Schmorl body. *b*, Roentgenogram. The arrow indicates a Schmorl body. (Coventry, M. B., Ghormley, R. K. and Kernohan, J. W.: *J. Bone & Joint Surg.* 27: 460 (July) 1945.)

cal changes in the intervertebral disk. The pathological changes consists of nuclear expansion, ballooning, thinning, Schmorl's bodies, anterior nuclear protrusion, posterior nuclear protrusion, calcified nucleus pulposus, invasion by infection and invasion by malignancy. Table I gives the frequency of the pathological changes encountered in the eighty-eight necropsy specimens. (Figs. 12,

sections of the disk and invasion by malignant tumors. Nuclear expansions are for the most part physiological and not pathological; whereas ballooned disks are found almost entirely in the disease entity known as senile osteoporosis of the spinal column.

"There are two types of thinned disks: One in which the cartilaginous plate and annulus are intact, the thinning being due to desiccation and necrosis of the nucleus pulposus, and the other type in which the annulus is ruptured, or the cartilaginous plate contains many de-



Fig. 13-A—Ballooned intervertebral disk ( $\times 3.5$ ) of a man, aged sixty years, suffering from osteoporosis. (Coventry, M. B., Ghormley, R. K. and Kernohan, J. W.: *J. Bone & Joint Surg.* 27: 460 (July) 1945.)

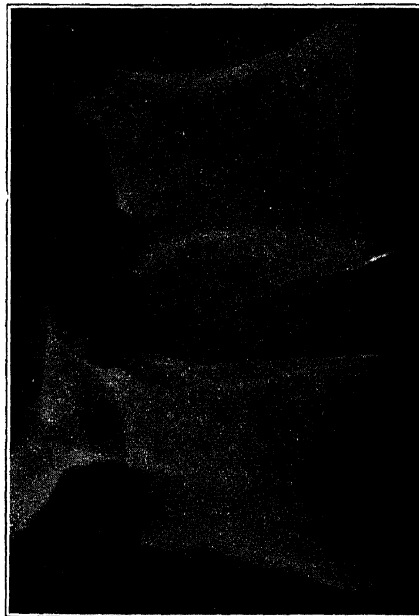


Fig. 13-B—Roentgenogram of the intervertebral disk shown in Fig. 13-A. (Coventry, M. B., Ghormley, R. K. and Kernohan, J. W.: *J. Bone & Joint Surg.* 27: 460 (July) 1945.)

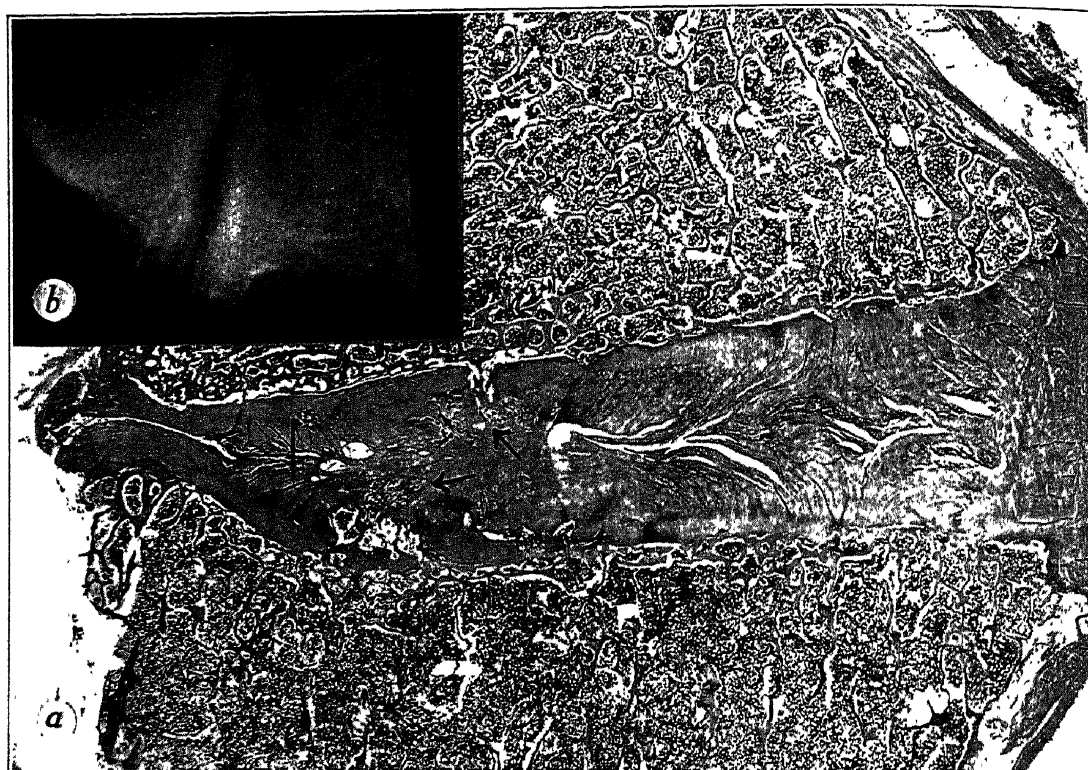


Fig. 14—Thinned intervertebral disk of a man, aged seventy years, with marked sclerosis of adjacent vertebrae. *a*, Section ( $\times 3.5$ ). Arrows point to invading blood vessels. There is posterior protrusion of nuclear material. *b*, Roentgenogram. (Coventry, M. B., Ghormley, R. K. and Kernohan, J. W.: *J. Bone & Joint Surg.* 27: 460 (July) 1945.)

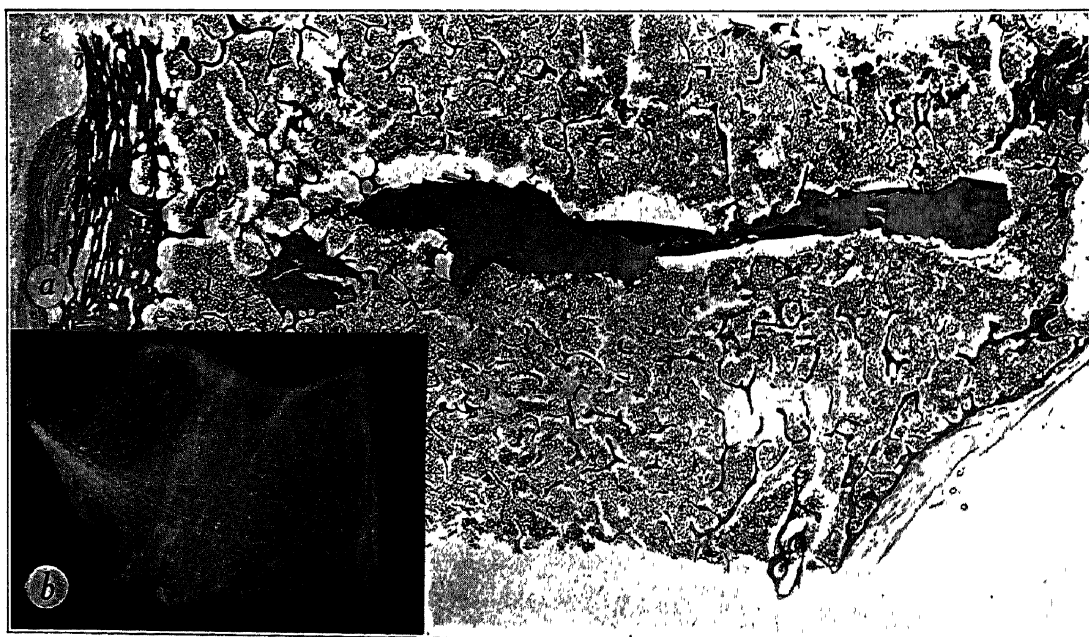


Fig. 15—Obliteration of intervertebral disk of a woman, aged sixty-five years, and consequent bony ankylosis. *a*, Section ( $\times 5$ ). *b*, Roentgenogram. (Coventry, M. B., Ghormley, R. K. and Kernohan, J. W.: *J. Bone & Joint Surg.* 27: 460 (July) 1945.)

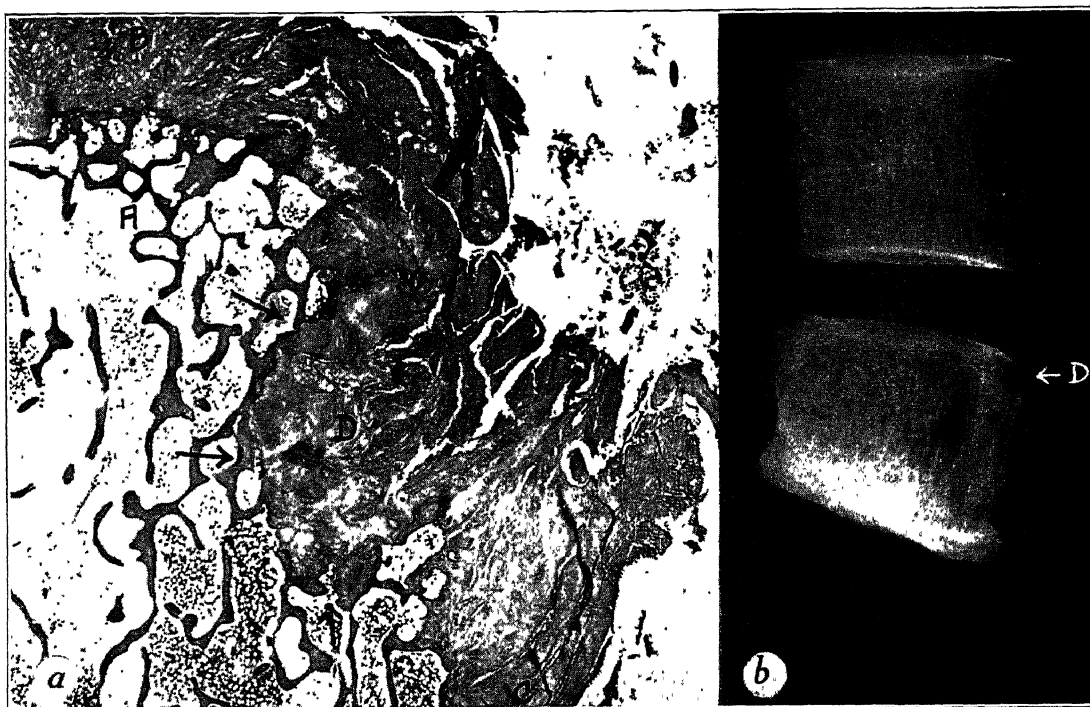


Fig. 16—Intervertebral disk of a woman, aged sixty-eight years. *a*, Section ( $\times 9$ ). *A*, Bony rim. *B*, Anterior portion of annulus fibrosus. *C*, Anterior longitudinal ligament. *D*, Protruded nuclear material. *b*, Roentgenogram. *D*, Protruded nuclear material. (Coventry, M. B., Ghormley, R. K. and Kernohan, J. W.: *J. Bone & Joint Surg.* 27: 460 (July) 1945.)

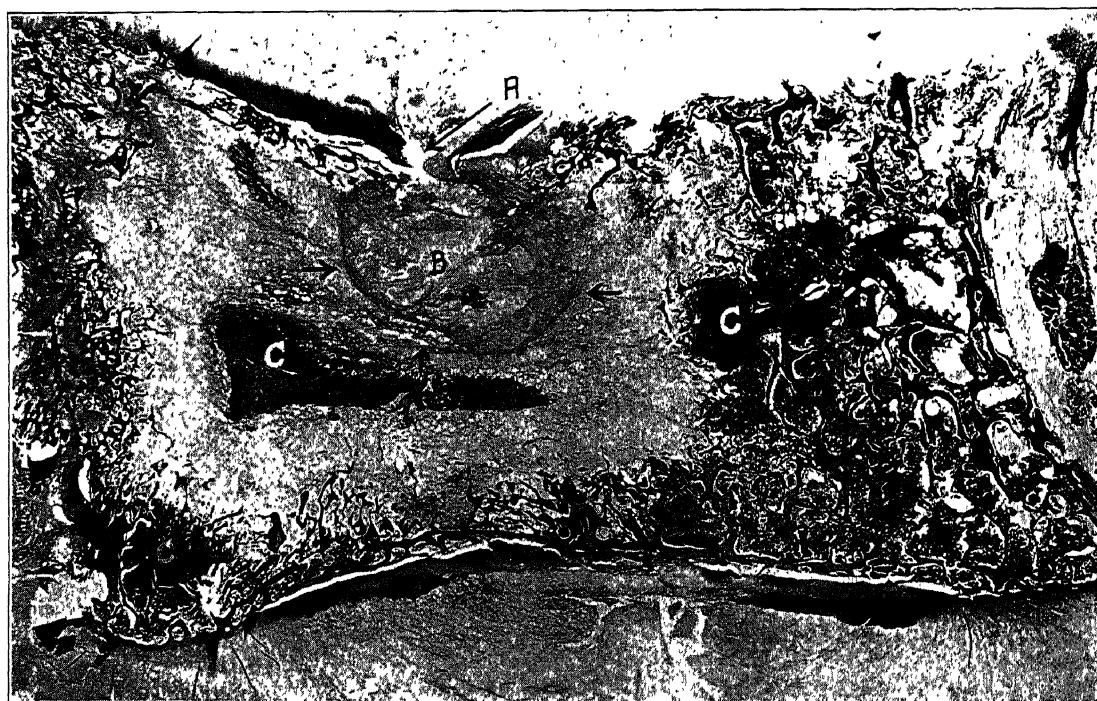


Fig. 17-A—Schmorl body in a vertebra of a man, aged seventy-five, suffering from metastatic carcinoma. *A*, Break in cartilaginous plate. *B*, Protruded nuclear material (Schmorl body). *C*, Metastatic carcinoma ( $\times 3.5$ ). (Coventry, M. B., Ghormley, R. K. and Kernohan, J. W.: *J. Bone & Joint Surg.* 27: 460 (July) 1945.)



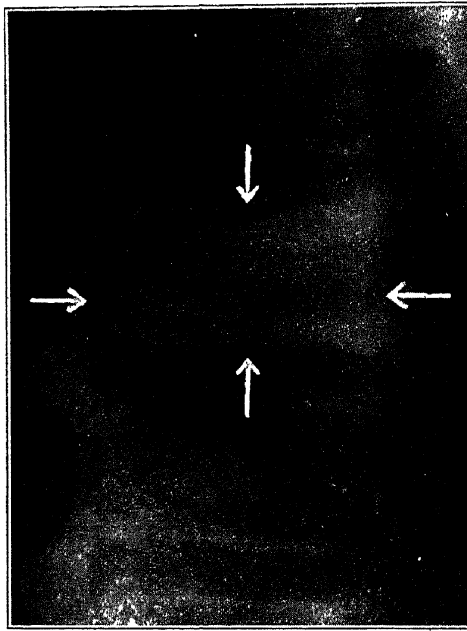


Fig. 17-B—Roentgenogram of the vertebra shown in Fig. 17-A. The arrows indicate the affected vertebra. (Coventry, M. B., Ghormley, R. K. and Kernohan, J. W.: *J. Bone & Joint Surg.* 27: 460 (July) 1945.)

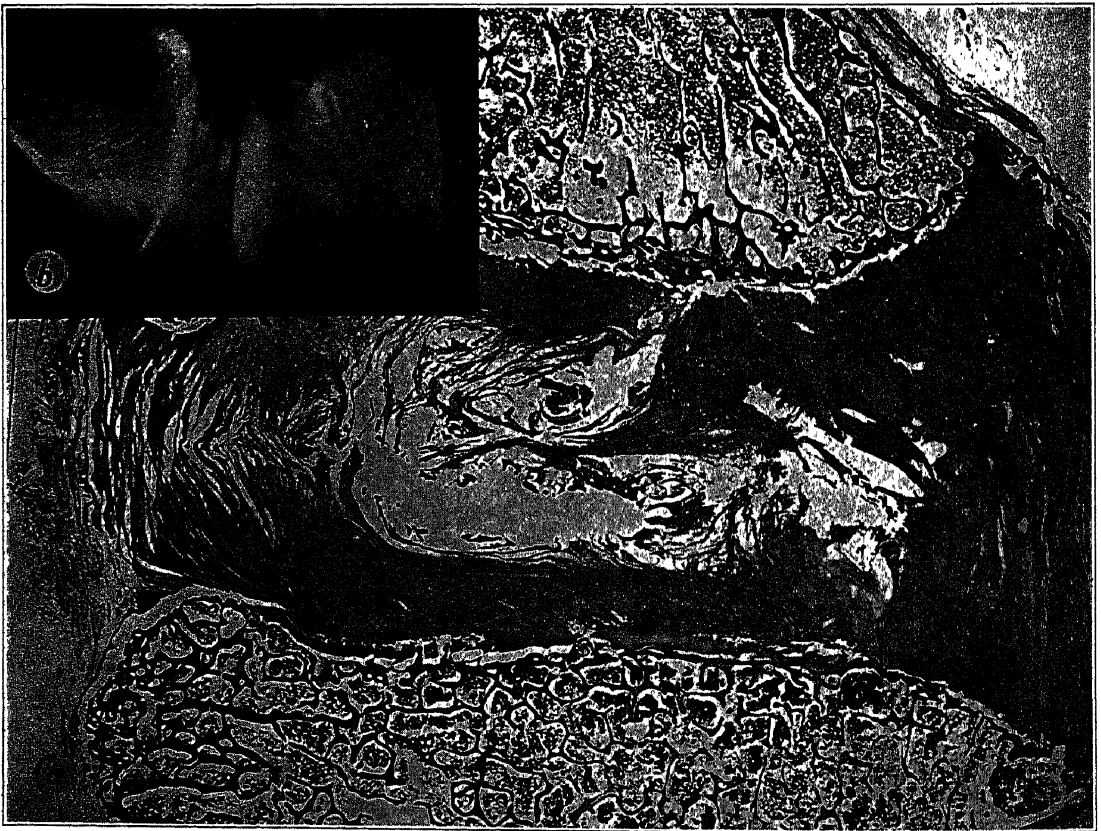


Fig. 18—Calcified nucleus pulposus of a woman, aged seventy-one years. *a*, Section ( $\times 4$ ). The calcium salts have been dissolved during preparation of the section, leaving space. *b*, Roentgenogram. (Coventry, M. B., Ghormley, R. K. and Kernohan, J. W.: *J. Bone & Joint Surg.* 27: 460 (July) 1945.)

fects. Dehydration is essentially the cause of thinning in both types.

"Intraspongy nuclear herniations or Schmorl bodies are for the most part asymptomatic. Anterior nuclear protrusions are rare and of little clinical interest, whereas posterior nuclear protrusions are of great clinical importance. Eight per cent of the specimens showed evidence of posterior nuclear protrusions.

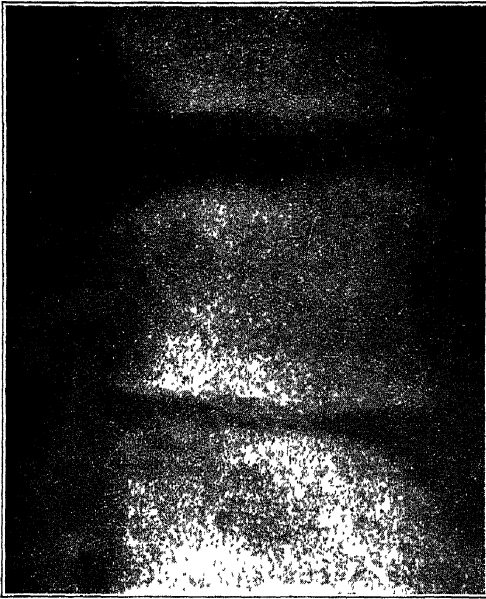


Fig. 19—Vertebral osteomyelitis, involving an intervertebral disk of a man, aged sixty-five years. (Coventry, M. B., Ghormley, R. K. and Kernohan, J. W.: J. Bone & Joint Surg. 27: 460 (July) 1945.)

"Calcification of the nucleus pulposus is a definite entity. However, it is of no clinical significance.

"Infection of the disk, resulting in early destruction of the annulus and nucleus, is recognized. The infection is usually blood-borne, and it may be primary or secondary to involvement of the vertebral body. The only example in this group was of infection of the disk, secondary to involvement of the vertebra.

"Invasion of the disk space by a malignant lesion is rarely found. Only one example was observed in this series, and in this case no real invasion of the cartilage was seen."

The work of Ghormley<sup>8</sup> is most highly commendable. This particular paper reports the third of a series of papers on

TABLE I

## INCIDENCE OF PATHOLOGICAL DISKS

<i>Pathological Changes</i>	<i>Number of Cases</i>
Nuclear expansion .....	7
Ballooning .....	5
Thinning .....	9
Intraspongy nuclear protrusions (Schmorl bodies)	
Microscopic .....	56
(Gross .....	5)
Anterior nuclear protrusions .....	1
Posterior nuclear protrusions .....	7
Calcified nucleus pulposus .....	1
Invasion by infection .....	1
Invasion by malignancy .....	1
<b>Total .....</b>	<b>88*</b>

\* Routine necropsy specimens, 85; added cases, 3.

(Coventry, M. B., Ghormley, R. K. and Kernohan, J. W. J. Bone & Joint Surg. 27: 460 (July) 1945.)

the intervertebral disk presented by the authors.

### March Fractures

The author<sup>9</sup> believes that a mild hypothyroid state may be the predisposing systemic cause in patients who develop March fractures. Fifty cases of March fractures were reviewed, of which forty-eight were studied from the standpoint of the basal metabolic rate. The average rate was  $-10.72$  per cent. The average pulse rate was 62. Treatment consisted of *bed rest* for a period of five days in twenty-four cases plus the administration of *desiccated thyroid*, 0.065 gm. (1 grain), three times a day for nineteen days. A test to distinguish the acute swelling of the fresh fracture from the later swelling produced by callus is called the pinch test and is described. This consists briefly of pinching the skin over the March fracture area. If the skin and overlying soft parts are sensitive, then the fracture is sensitive.

If they are not sensitive, then the fracture is not a fresh one and the swelling is due to callus of a healing fracture.

The possibility of hypothyroidism affording a pathological basis for the insufficiency in March fractures must be given serious consideration. It ranks among the most outstanding valuable contribution towards the solution of this mysterious fracture.

tion of the fracture surfaces. Figs. 21 and 22 are illustrative of the preparation and the function of the screw. Seventeen cases were reviewed after a post-operative lapse of one to four years. The standard for a successful result was considered to be bony union with a minimum necrosis of the femoral head, good function, with a history of walking with comfort and freedom from pain.

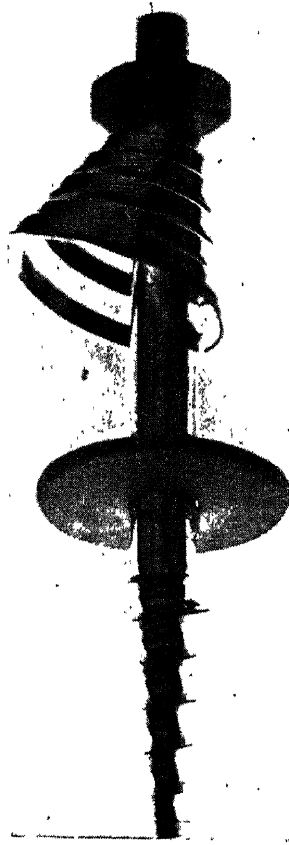


Fig. 20—The continuous traction screw. (Virgin, H., Jr. and MacAusland, W. R.: *Ann. Surg.* 122: 59 (July) 1945.)

### Continuous Traction Screw for Fixation of Fractures of the Hip

Virgin and MacAusland<sup>10</sup> present a continuous traction screw, Fig. 20. The appliance embodies a new feature consisting of a special spring arrangement that provides for take-up in the event of absorption about the fracture line in the hope of maintaining continuous apposi-

Clinically, twelve of the seventeen cases obtained results embodying these requirements.

The above represents another attempt to improve the results of internal fixation. The principle of maintaining contact would appear sound, providing rigid fixation is not sacrificed because of the spring. Furthermore, it should be em-



phasized by the authors that the continuous traction screw is not a substitute for a poor reduction.

### Treatment of Malunited Colles' Fractures

Speed and Knight<sup>11</sup> present a brief résumé as well as illustrations of various procedures employed in the treatment of

*Group 1*—This group includes cases in which the deformity consists chiefly of a dorsal tilting of the distal articulating surface of the radius associated with little or no radial shortening. The treatment consists of a simple osteotomy of the radius without internal fixation.

*Group 2*—The malunion consists of a broadening of the wrist due to radial

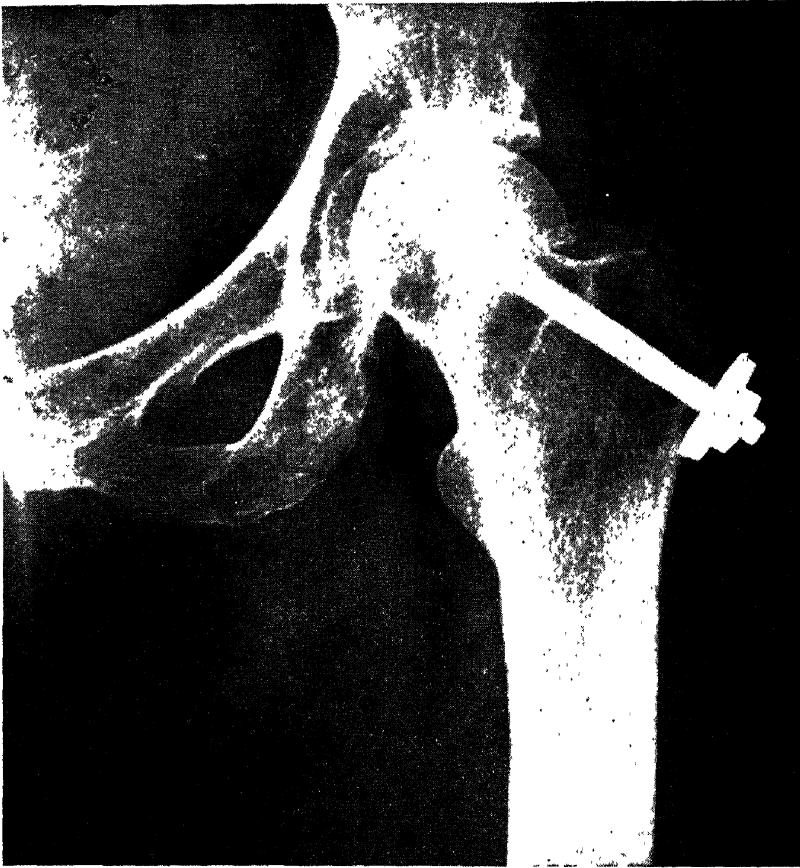


Fig. 21—Roentgenogram of a case in which there was no absorption of the femoral neck, and, hence, no expansion of the spring. (Virgin, H., Jr. and MacAusland, W. R.: *Ann. Surg.* 122: 59 (July) 1945.)

malunited Colles's fractures. The objectives of the surgical correction are to restore the normal anatomy as nearly as possible, improve the function of the part by compensatory procedures such as resection of the distal end of the ulna, and improvement in the appearance of the wrist itself. They have divided the malunited Colles's fractures into six groups.

shortening and associated prominence of the ulnar head. The operative procedure consists of an osteotomy of the malunited radius at the old fracture site and a resection of the oblique portion of the prominent ulnar head, employing this material as a graft to maintain the reduction of the fracture (Figs. 23A and 23B).

*Group 3*—Malunion is more severe and can be adequately corrected by either of the above procedures and in such instances the use of a homogenous or autogenous intermedullary bone peg is employed. (Figs. 24*A* and 24*B*.)

*Group 4*—In this group a heavy onlay graft fixed by two vitallium screws or the dual bone graft were employed in preference to the procedures used in group 3. (Figs. 25*A* and 25*B*.)

*Group 5*—Malunion in which the de-

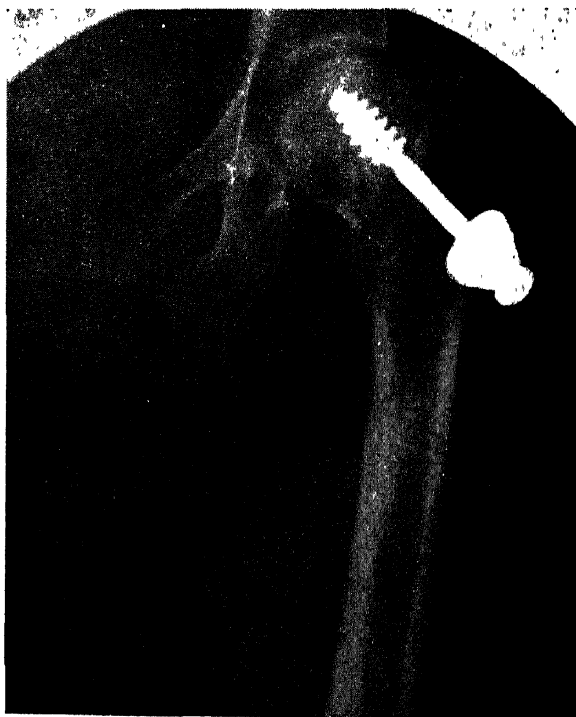


Fig. 22—Roentgenogram of a case with destruction of the femoral neck, in which the spring took up approximately seven eighths of an inch of absorption. (Virgin, H., Jr. and MacAusland, W. R.: *Ann. Surg.* 122: 59 (July) 1945.)



Fig. 23-A—Mrs. J. C. R., No. 41182. Malunited Colles' fracture, with good functional but poor cosmetic result. (Speed, J. S. and Knight, R. A.: *J. Bone & Joint Surg.* 27: 361 (July) 1945.)



Fig. 23-B—Radial deformity corrected by ulnar graft, wedged into radial osteotomy site. Prominent portion of ulna was removed for cosmetic reasons and used as graft. (Speed, J. S. and Knight, R. A.: *J. Bone & Joint Surg.* 27: 361 (July) 1945.)

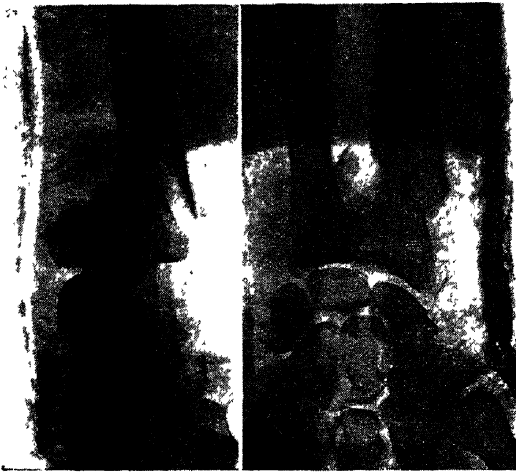


Fig. 24-A—Mr. L. A. L., No. 57648. Unstable compound Colles' fracture, with delayed union in malposition. (Speed, J. S. and Knight, R. A.: *J. Bone & Joint Surg.* 27: 361 (July) 1945.)



Fig. 24-B—Result one year after operation. Lower end of ulna was resected, permitting reduction of radial displacement; homogenous bone peg was used for stability of radial fracture. Excellent functional result, with exostosis, but not synostosis, of ulna. (Speed, J. S. and Knight, R. A.: *J. Bone & Joint Surg.* 27: 361 (July) 1945.)

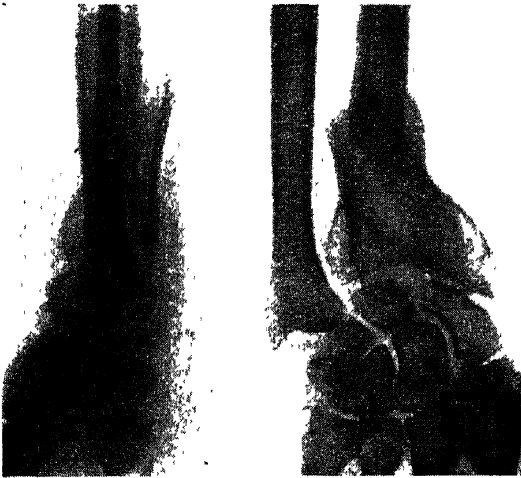


Fig. 25-A—Mr. D. R., No. 57966. Malunion of oblique comminuted Colles' fracture, with radial shortening and ulnar prominence. Marked inferior radioulnar displacement. (Speed, J. S. and Knight, R. A.: *J. Bone & Joint Surg.* 27: 361 (July) 1945.)



Fig. 25-B—Result after step-cut osteotomy to gain radial length, and resection of lower end of ulna to correct discrepancy in length of radius and ulna. Resected portion of ulna was used as dorsal radial graft. (Speed, J. S. and Knight, R. A.: *J. Bone & Joint Surg.* 27: 361 (July) 1945.)



Fig. 26-A—Mr. W. K., No. 40540. Mal-united Colles' fracture after failure of reconstructive procedure. (Speed, J. S. and Knight, R. A.: *J. Bone & Joint Surg.* 27: 365 (July) 1945.)



Fig. 26-B—Result six months after fusion of wrist. Function was much improved, despite insufficient resection of ulna. (Speed, J. S. and Knight, R. A.: *J. Bone & Joint Surg.* 27: 365 (July) 1945.)

formity is situated close to the articulating surface, and here there is marked osteoporosis or severe comminution of the distal fragment. (Figs. 26A and 26B.) An arthrodesis of the wrist is performed usually combined with a resection of the distal end of the ulna.

*Group 6*—In cases of malunion in which the chief source of the disability is an inferior radioulnar traumatic arthritis. Resection of the distal end of the ulna alone will suffice. (Figs. 27A and 27B.)

This presentation is of value in that it emphasizes the need for careful reduction of the so-called Colles' fracture. It also calls attention to the complications associated with malunion and points out the numerous variations. A method of correction is clearly outlined in each instance.



A

B

Fig. 27-A—Mr. O. R., No. 59369. Old fracture of distal end of radius, with injury of inferior radioulnar articulation. There was severe disability, due to pain in radioulnar joint. (Speed, J. S. and Knight, R. A.: *J. Bone & Joint Surg.* 27: 367 (July) 1945.)

Fig. 27-B—Resection of distal end of ulna completely relieved pain and disability. (Speed, J. S. and Knight, R. A.: *J. Bone & Joint Surg.* 27: 367 (July) 1945.)

### Anterior Transposition of the Peroneal Nerve for Traction Paralysis

Milch<sup>12</sup> calls attention to the peroneal palsy associated with excessive traction, occurring during the process of reduction of a fracture of the tibia, or as a

around the tibial head of the peroneus longus. But even more important than this is its relationship to the fascia lata, which lies superficial to the peroneus longus muscle and takes a firm attachment to the fibular head at a point just above and slightly more lateral to the origin of the long head of the peroneus longus. Both the muscle and the fascial attachment act

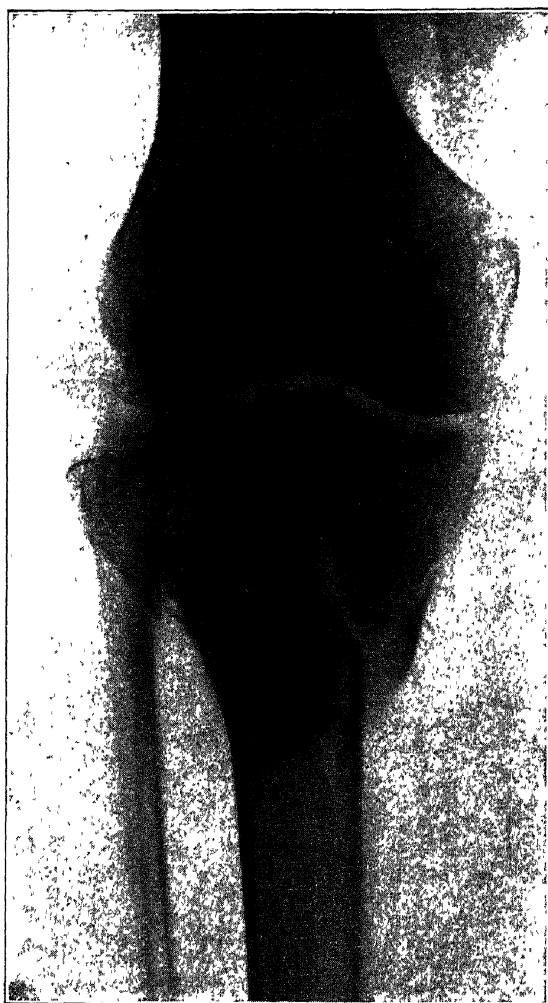


Fig. 28-A—Comminuted fracture with increased tibiofibular distance due to the increase in the width of the tibial condyles. (Milch, H.: *J. Bone & Joint Surg.* 27 : 608 (Oct.) 1945.)

result of the traction, produced by the angulation or displacement of the fragments themselves (lateral strain). The author cites early observations by Platt, Watson-Jones, Highet, Holmes, and others.

"The peroneal nerve winds around the neck of the fibula, making an almost right-angle turn

as a fulcrum around which the nerve changes its course. Since the nerve is covered by the deep fascia, this kneelike change in direction acts as a fixed point against which traction may be exerted."

Varus strain at the knee with gradual onset, or acute, may produce evidence of peroneal nerve neurology.

In summary, the author states that excessive traction on the peroneal nerve with resulting paralysis may be eliminated by transplanting the nerve forward. This is usually accomplished by detaching the tibial head of the peroneal longus muscle. In case the transplant

often than is generally appreciated. Due to the absence of crural pain or radiological changes, the resulting lesion is often mistaken for sacroiliac strain or fibrositis. The condition may be easily recognized by persistent and extreme lumbar spasm and a tight lumbar spine.

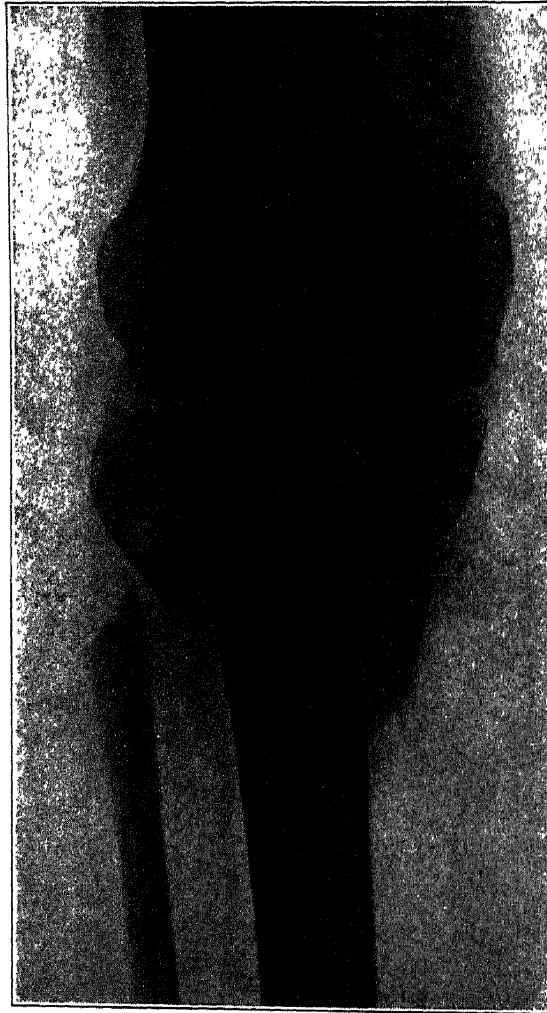


Fig. 28-B—Same as Fig. 28-A, after resection of the fibular head to accommodate the peroneal nerve. (Milch, H.: *J. Bone & Joint Surg.* 27: 608 (Oct.) 1945.)

is unsuccessful, resection of the fibular head is indicated. Figs. 28A and 28B are illustrative of the possible causes and the cure of the stretch palsy.

#### Damaged Intervertebral Disk

The author<sup>13</sup> believes that intervertebral disks suffer trauma far more

(Figs. 29 and 30.) He rightfully points out that early diagnosis and treatment by immobilization should reduce considerably the incidence of sciatica.

"Cases which escape diagnosis until after the onset of sciatic pain may be divided into two groups, depending on whether the annulus fibrosis is partially

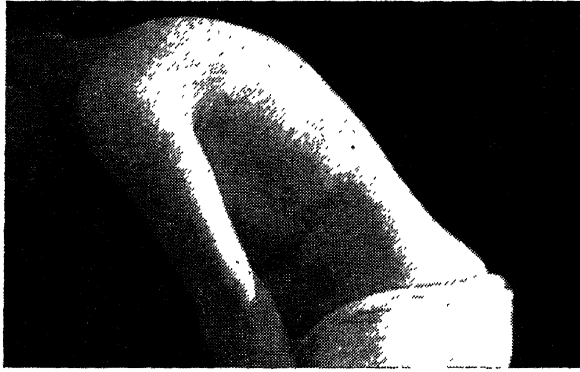


Fig. 29—Typical case of damaged intervertebral disk of two months' duration, showing limitation of forward flexion. (Crisp, E. J.: *Lancet* 2: 422 (Oct. 6) 1945.)

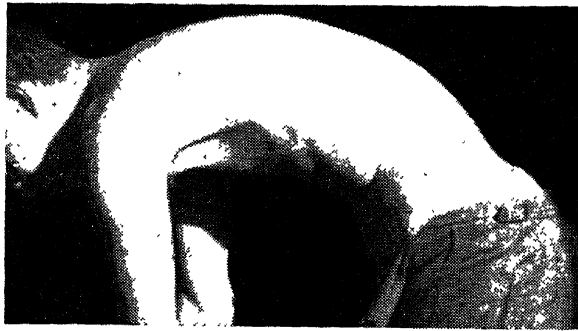


Fig. 30—A "healed" disk: Spine had been immobilized in plaster jacket nine months previously. Patient is now free from pain, and normal range of flexion has returned except at the site of the lesion (lower lumbar vertebra). (Crisp, E. J.: *Lancet* 2: 422 (Oct. 6) 1945.)



Fig. 31—Typical lumbar kyphosis after damaged intervertebral disk. (Crisp, E. J.: *Lancet* 2: 422 (Oct. 6) 1945.)



Fig. 32—Plaster jacket applied in a case of damaged intervertebral disc. (Crisp, E. J.: *Lancet* 2: 422 (Oct. 6) 1945.)

or completely ruptured. The former group may be recognized by the fixed lumbar lordosis and the latter by the fixed lumbar kyphosis. Both groups usually respond well to immobilization in a spinal jacket." (Figs. 31 and 32.)

### Immediate Skin Grafting Following Injuries

Through the use of skin grafting, many open wounds can be converted into closed wounds and thus primary healing obtained. Primary healing means

between the graft and its bed; (4) improper or inadequate anchorage of the graft so as to allow movement during the healing period. A variety of injuries is described in some detail with methods of graft best suited to each type.<sup>14</sup>

### Para-articular Calification (Pelligrini-Stieda) in Affections of the Knee

Nachlas and Olpp<sup>15</sup> point out an extremely important point in this composition. "The imposing name of Pelligrini-

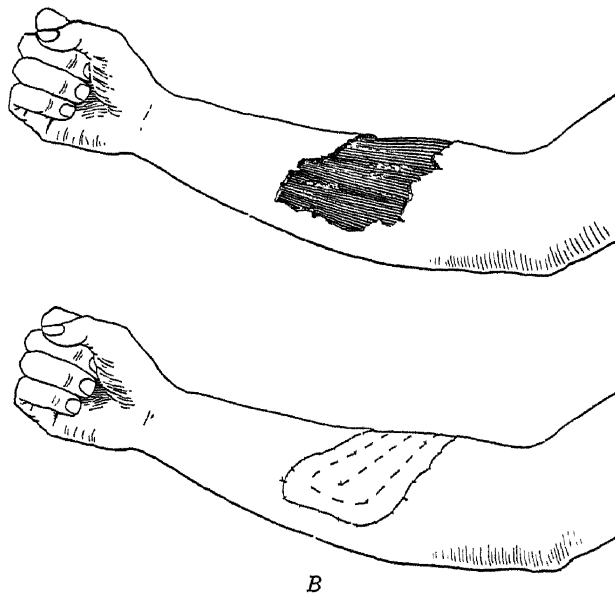


Fig. 33—*A*, above, Wound of forearm in which the superficial structures have been torn away down to the muscle. *B*, below, After thorough surgical cleaning and débridement wound has been converted into a "closed wound" by means of a partial thickness graft. The graft is 0.018 inch and was taken from the thigh with a Padgett dermatome. Note the basting type of suture which is used to hold the graft in firm apposition with underlying tissues and which also allows escape of serum. All sutures are fine black silk. (King, M. K.: Surg., Gynec. & Obst. 81: 75 (July) 1945.)

a tremendous economic saving as well as decreased pain, improved function, and superior cosmetic results.

To be successful, all dirty wounds must be surgically clean before grafting is attempted. Grafts must be placed and held in firm apposition with the underlying tissue. The most common causes of failure in skin grafting are (1) infection; (2) blood or serum pockets beneath the graft; (3) inadequate contact

Stieda disease is misleading. It implies that the one finding of calcification over the adductor tubercle is a disease complex. The stress that is given this particular manifestation tends to detract from what is usually the significant part of the patient's disease, namely, the arthritis of the knee joint."

Twenty cases were studied with calcification overlying the adductor tubercle of the femur. In no instance were there



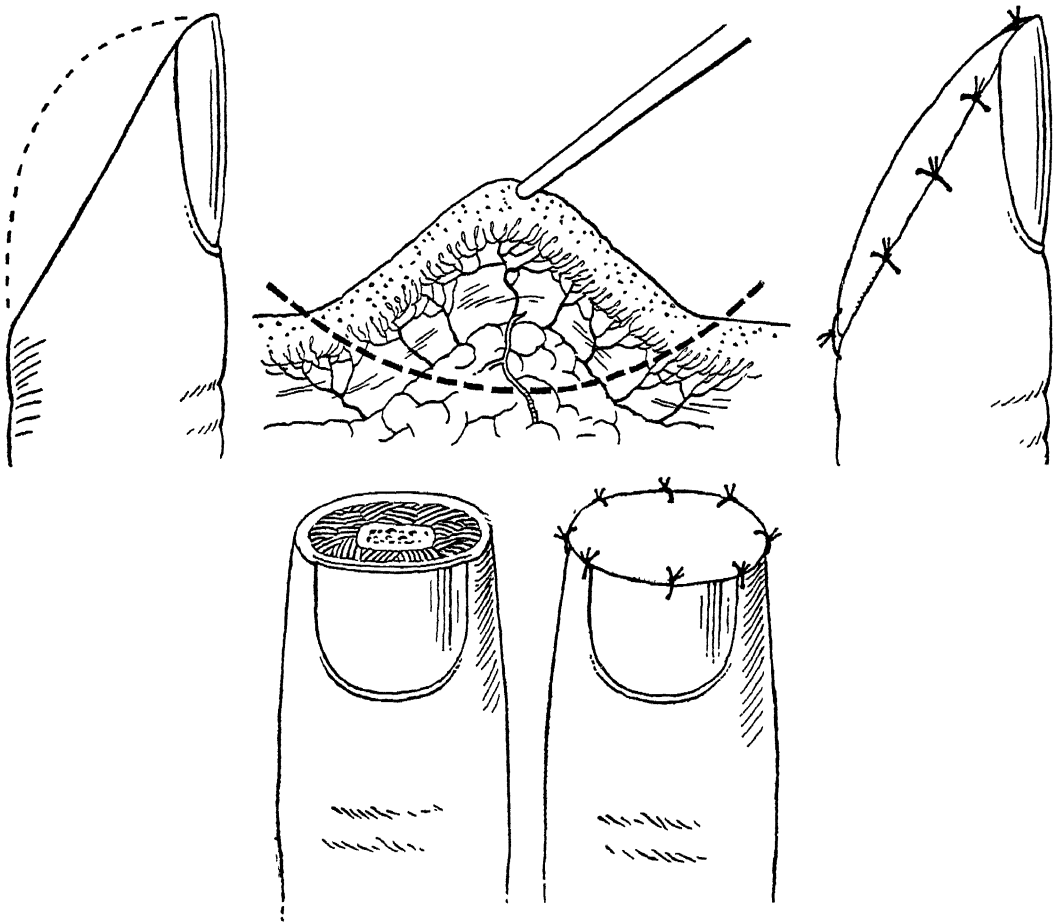


Fig. 34—Slicing wounds of the fingertips, covering immediately with a small thick graft. The graft is thick at the center, tapered at the edges, and is cut from the forearm with a scalpel. Sutures are of fine silk. (King, M. K.: Surg., Gynec. & Obst. 81:75 (July) 1945.)

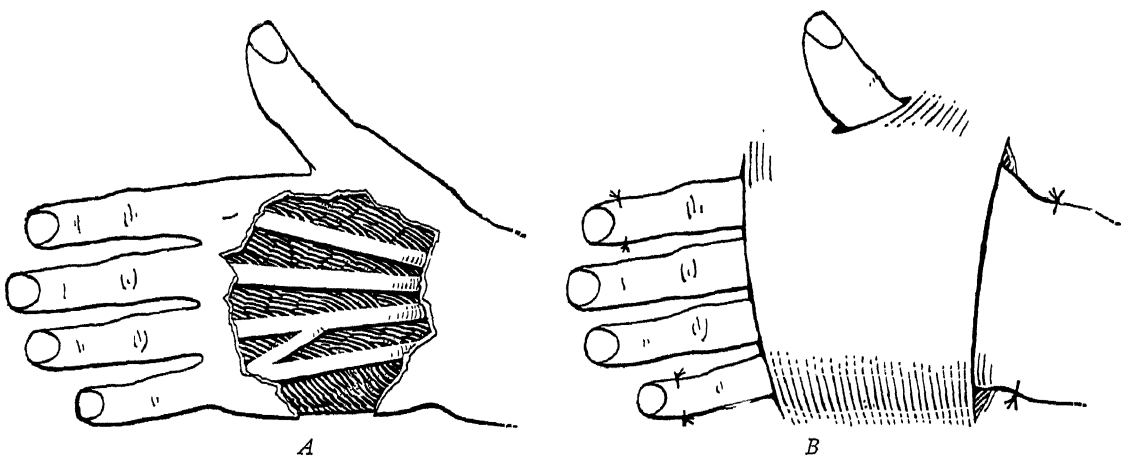


Fig. 35—*A*, left, Wound of the dorsum of hand leaving extensor tendons exposed. If the tendons are not covered, sloughing may be expected with crippling and deformity. A partial thickness graft will not give good function. *B*, right, After surgical cleansing and débridement, the hand has been placed in a pocket flap on the abdomen. The flap is thick and carries some fat. Note the anchor sutures to prevent movement of the hand. One end of the flap is divided in seven to ten days, the other in twelve to seventeen days. The abdominal defect is covered with a partial thickness graft. (King, M. K.: Surg., Gynec. & Obst. 81:77 (July) 1945.)

complaints regarding the knee because of the calcification. This convinces the authors that Pelligrini-Stieda disease, so called, is of little clinical importance other than to be recognized as a harmless finding. In cases in which there was a complaint referable to the knee, it was found invariably to be due to some other cause, usually arthritis. Figs. 36 and 37 consist of radiographs showing rather typical para-articular calcifications (Pelligrini-Stieda disease).

frozen shoulder under anesthesia, the capsule is separated from the head much the same way that adhesive plaster can be torn away from the bare skin. Once this separation has occurred, motion in the joint is free."

The author suggests that the name "adhesive capsulitis" be substituted for the commonly used expression "frozen shoulder." His studies are based on ten live patients and sixty-three shoulders of thirty-six patients who died from

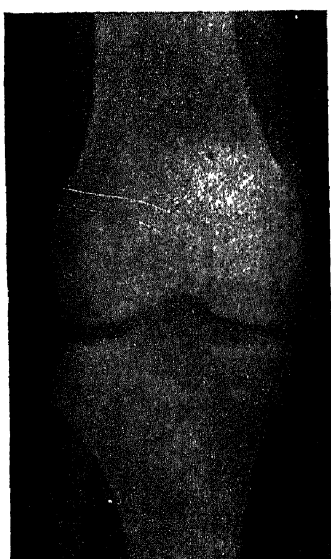


Fig. 36.



Fig. 37.

Fig. 36—Roentgenogram of right knee showing the extra-articular ossification overlapping the adductor tubercle. (Nachlas, I. W. and Olpp, J. L.: *Surg., Gynec. & Obst.* 81: 207 (Aug.) 1945.)

Fig. 37—Roentgenograms showing calcified mass medial to area of adductor tubercle at some distance from the tibial collateral ligament and separated from cortex by radiolucent line. (Nachlas, I. W. and Olpp, J. L.: *Surg., Gynec. & Obst.* 81: 207 (Aug.) 1945.)

### Adhesive Capsulitis of the Shoulder

The author<sup>16</sup> is of the impression that the so-called frozen shoulder is due to a thickening and contraction of the capsule of the shoulder joint, the latter becoming adherent to the humeral head. A microscopic section confirms the presence of reparative inflammatory changes in the capsule (Figs. 38, 39A, and 39B). In some cases there are also similar changes in the wall of the subacromial bursa. "During manipulation of the

various causes (autopsy studies). With one exception the x-ray findings of the ten patients selected for operation were entirely negative (exception—calcification in the short rotator cuff). All patients had pain with limitation of motion on abduction, internal rotation, and external rotation. Forward flexion and backward extension were painless and not limited. The adhesion of the capsule was found in all ten cases and the effects of the manipulation were observed at the



Fig. 38—Case 8. Photomicrograph ( $\times 80$ ) of capsule shows (a) degeneration of collagen of the subsynovia and (b) vascular dilatation and perivascular infiltration. (Neviaser, J. S.: *J. Bone & Joint Surg.* 27: 211 (April) 1945.)

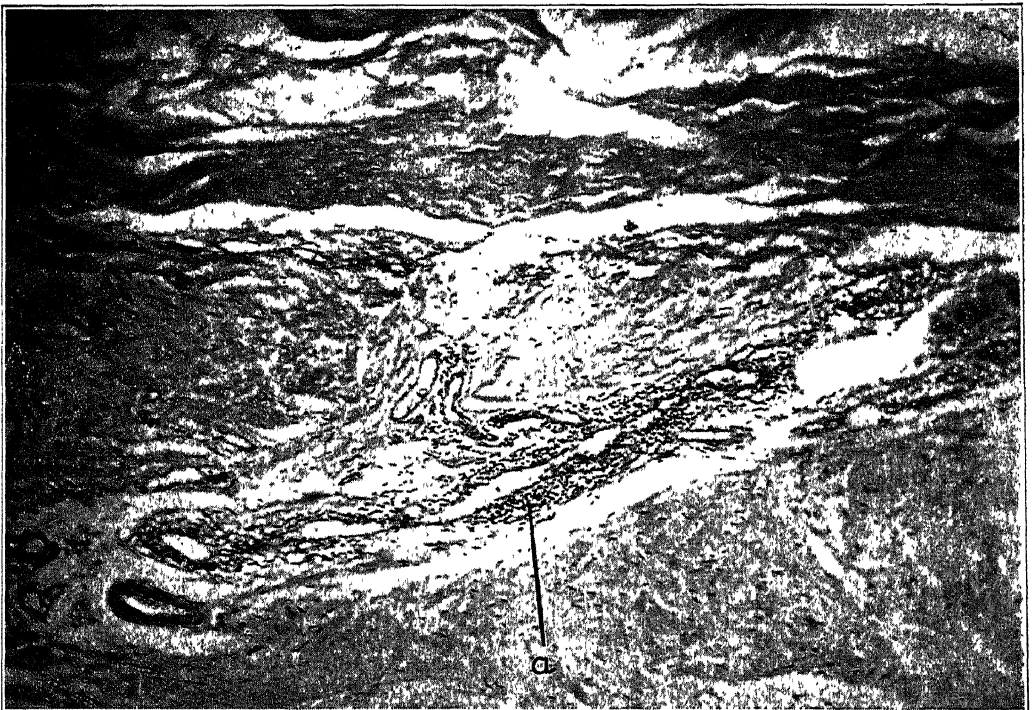


Fig. 39-A—Case 9. Photomicrograph ( $\times 80$ ) shows (a) perivascular lymphocytic infiltration in the capsule. (Neviaser, J. S.: *J. Bone & Joint Surg.* 27: 211 (April) 1945.)

time of the operation. Routine cultures were negative.

Neviaser's work is worth while in that it again calls our attention to the pathology of the so-called stiff shoulder. The findings afford a better basis for manipulative therapy of the shoulder, which is one of the principal measures in the therapy of this very disabling and painful condition.

seventeen of which had developed bone sarcoma following heavy roentgenotherapy for tuberculous arthritis. Figs. 40A, 40B, and 40C are illustrative of one of the writer's three cases. Fig. 40B shows an apparently healed benign chondroblastoma of the tibia. The upper end of the fibula is surrounded by a mass of variable density which proved to be sarcoma at biopsy. Fig. 40C shows a large

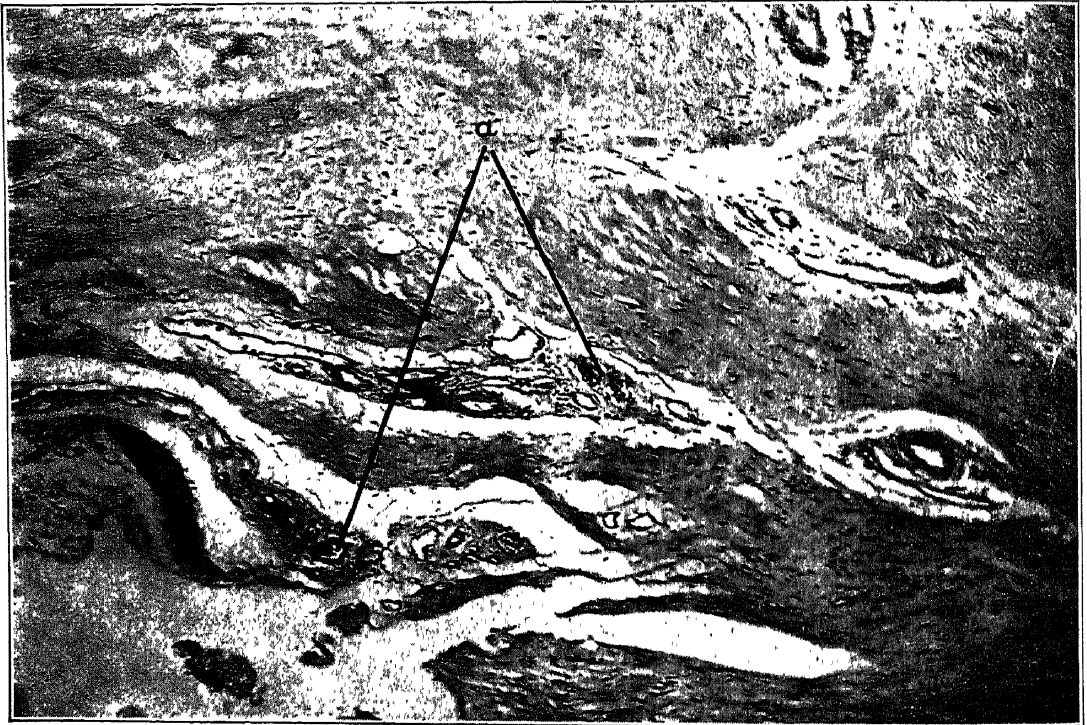


Fig. 39-B—Case 9. Photomicrograph ( $\times 80$ ) of another section of capsule showing (a) perivascular lymphocytic infiltration (Neviaser, J. S.: *J. Bone & Joint Surg.* 27 : 211 (April) 1945.)

### Development of Sarcoma in Bone Subjected to Roentgen or Radium Irradiation

The author<sup>17</sup> presents three patients in whom irradiation appears to be responsible for the development of bone sarcoma. In each case the tumor arose in normal bone which had been in the field of irradiation directed toward an independent lesion. In addition to the above three cases, twenty-one additional cases were collected from the literature,

metastatic tumor mass in the hilum of the right lung, ten months after thigh amputation. Hatcher's presentation is of tremendous value in that it calls attention to the danger of prolonged roentgenotherapy and radium therapy.

### Delayed Primary Closure of Wounds With Compound Fractures

The authors<sup>18</sup> present a review of 2393 closures of wounds in compound fractures with 93 per cent healed. Their recommendations are as follows: Early

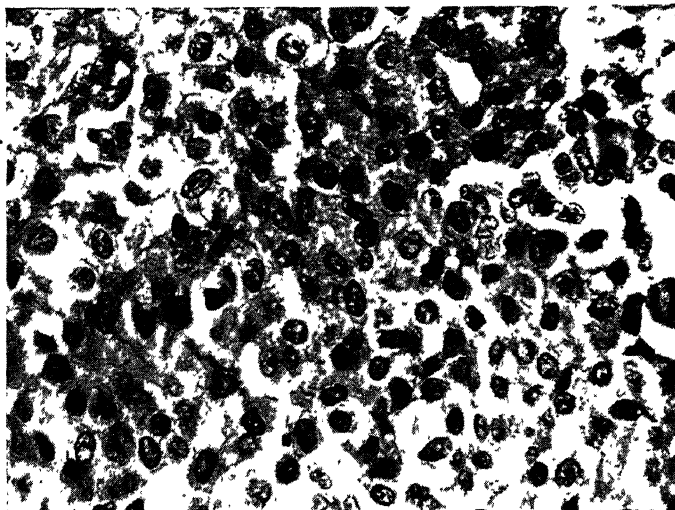


Fig. 40-A—Case 1. Photomicrograph ( $\times 300$ ) of epiphyseal chondroblastoma of tibia.  
(Hatcher, C. H.: J. Bone & Joint Surg. 27:179 (April) 1945.)



Fig. 40-B—Roentgenograms four years after last roentgen exposure show: irregular sclerosis at site of original epiphyseal tumor of tibia; partial destruction and replacement of the proximal end of fibula by mass of variable density. (Hatcher, C. H.: J. Bone & Joint Surg. 27:179 (April) 1945.)

and adequate surgical débridement of the wound; transfusions; high calorie and vitamin diet as an aid to general systemic improvement. Most of the wounds referred to were closed between the eighth and thirteenth days.

The importance of this article lies in the fact that compound fractures in civilian life should be given equally

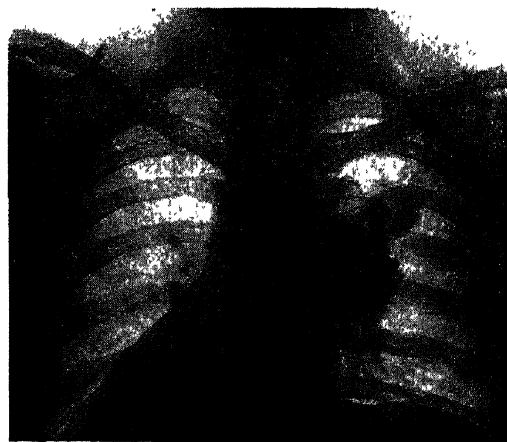


Fig. 40-C—Roentgenogram of chest ten months after thigh amputation shows metastatic tumor mass near the hilum of right lung. (Hatcher, C. H.: *J. Bone & Joint Surg.* 27: 179 (April) 1945.)

serious consideration. Thorough débridement, immobilization, and secondary primary closure at the earliest possible moment seem justified. The general condition of the patient must not be lost sight of and any difficulty should be supplemented by adequate chemotherapy, diet, transfusions, etc.

### Congenital Stricture of the Spinal Canal

The author<sup>19</sup> is of the impression, in fact, reasonably sure, that congenital stricture or narrowing of the spinal canal is responsible for many cases of enuresis, club foot, and spastic and flaccid paralysis, leading to abnormalities of gait and contractures. "The narrowing of the bony canal compresses the cord, and, by

the law of Delpech, prevents it from normal development. It is also probable that there are congenital strictures of the intervertebral foramina which cause pressure against the nerve-roots. These lesions, unlike those in later life, do not cause pain, since they develop very slowly and tend to inhibit growth of the nerve, whereas the inflammatory constrictions of later life cause sudden pressure against a fully developed nerve, and are, therefore, painful."

The author lists the following forms of congenital stricture of the spinal canal:

"1. A narrowing of the canal, forming a ringlike constriction of the cord at one or more levels. This variety is usually found in cases of enuresis, and is readily cured by laminectomy. Relief comes within a few hours of operation.

"2. More extensive strictures, involving an entire region of the canal. This type is usually associated with spastic paralysis similar to that seen in Little's disease.

"3. A localized stricture, causing compression of the spine and paralysis of certain groups of muscles. This is the type responsible for club foot.

"4. Atypical cases, causing a cleft either in the cord alone or in both cord and dura mater."

Spina bifida occulta, according to the author, is almost invariably associated with the narrowing of the canal, "in fact, 56 per cent of the cases of urinary calculi in Turkey, which were caused by a long-continued cystitis, were due to stricture of the spinal canal" associated with spina bifida occulta. Figs. 41A, 41B, 42C, 42D, 42E, and 42F are illustrative.

It is the author's opinion that it will rest with the neurologist and the neurosurgeon to determine the true value of Sarpyener's work. The association of cord neuropathy with congenital anom-

alties of the lower extremities and, for that matter, of the upper extremities is by no means a new thought and has been offered as one of the explanations of congenital deformities in the earliest medical treatises on the subject. In recent years, particularly the twentieth century, very little attention has been given this subject. The work of this

of the spine secondary to rheumatoid arthritis. (Fig. 44A.) The osteotomy is best illustrated by Figs. 43, 44C, and 44D. Figs. 44A and 44B are photographs and show the degree of correction obtained.

One of the authors, Smith-Petersen, has been interested in the restoration of joint movement in the correction of de-

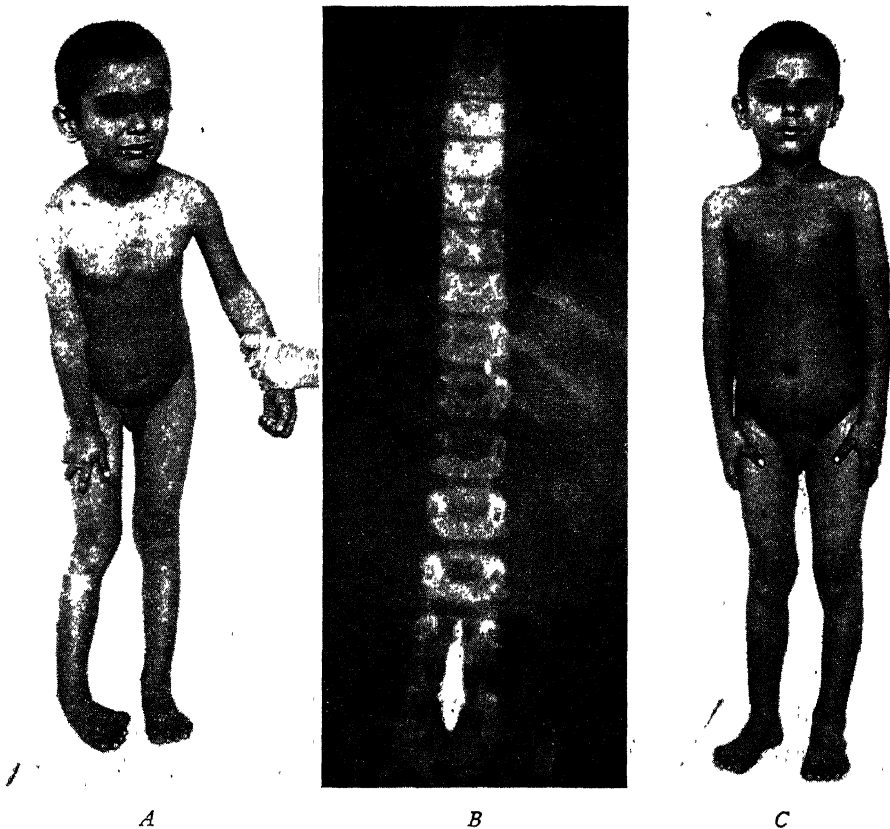


Fig. 41—A, Case. 7. Rustem. Showing patient before laminectomy. B, After suboccipital injection, the lipiodol remained at the first sacral vertebra, where there was no spina bifida occulta. C, Showing patient after laminectomy. (Sarpyener, M. A.: J. Bone & Joint Surg. 27: 70 (Jan.) 1945.)

author again revives this approach to the various orthopedic and neurological conditions which he has listed.

#### **Osteotomy of the Spine for Correction of Flexion Deformity in Rheumatoid Arthritis**

The authors<sup>20</sup> suggest an osteotomy for the correction of a flexion deformity

formities in rheumatoid arthritis for many years. He has contributed a number of excellent articles pertaining to this subject, among which may be listed the acromioplasty for the stiff shoulder, the vitallium cup arthroplasty for stiff hips, etc. The osteotomy of the spine is a practical one (has been employed by the reviewer on one case with most satisfac-





Fig. 42-A—Before laminectomy, the patient was able to stand up only by leaning on the wall.



Fig. 42-B.

Fig. 42-C.

Fig. 42-B—Roentgenogram shows spina bifida occulta.

Fig. 42-C—Twenty-four hours after suboccipital lipiodol injection, the lipiodol remained at the second, third, and fourth lumbar vertebrae.

(Sarpyener, M. A.: J. Bone & Joint Surg. 27: 70 (Jan.) 1945.)



Fig. 42-D—Four months after laminectomy, the patient can stand up and walk slowly without leaning on anything.

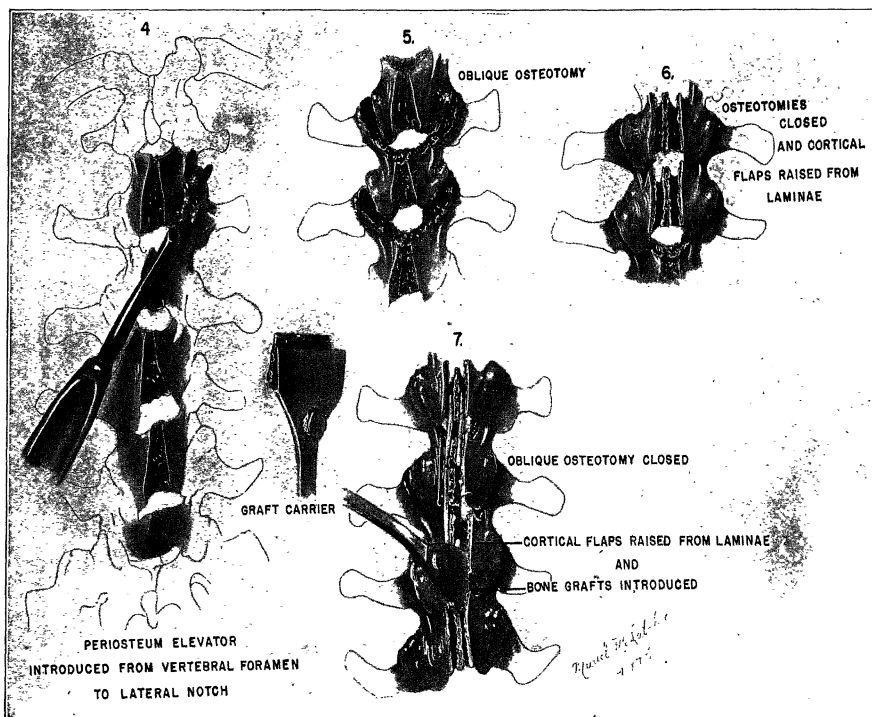


Fig. 43—4, Periosteum elevator has been introduced anterior to lamina and articular process; its point is seen at the intervertebral or lateral notch. 5, The oblique osteotomy has been completed at two levels. (The diagram is correct, but is misleading in so far as the space created is concerned—there should be a space of one-quarter to three-eighths of an inch between the osteotomy surfaces.) 6, The head and foot of the operating table have been raised and the osteotomy spaces have been closed. Cortical lamellae have been raised from the laminae. 7, Bone grafts, obtained from the spinous processes, have been introduced into the laminae. The bone-graft carrier is shown in position. (Smith-Petersen, M. N., Larson, C. B. and Aufranc, O. E.: J. Bone & Joint Surg. 27: 1 (Jan.) 1945.)



tory results). The authors bring out a number of important points, namely, that surgical intervention in rheumatoid arthritis should be undertaken early before secondary deformities develop; that is, a flexion deformity of the spine frequently results in delayed surgical treatment of the hips (arthroplasty). Six

and supplementing the *vasta medialis* with the *semitendinosus*. Figs. 45A and 45B are illustrative. The procedure has been performed on twenty-three cases, twenty in children under sixteen and three in adults. Satisfactory function has been restored in all the joints and no recurrent dislocations have followed.

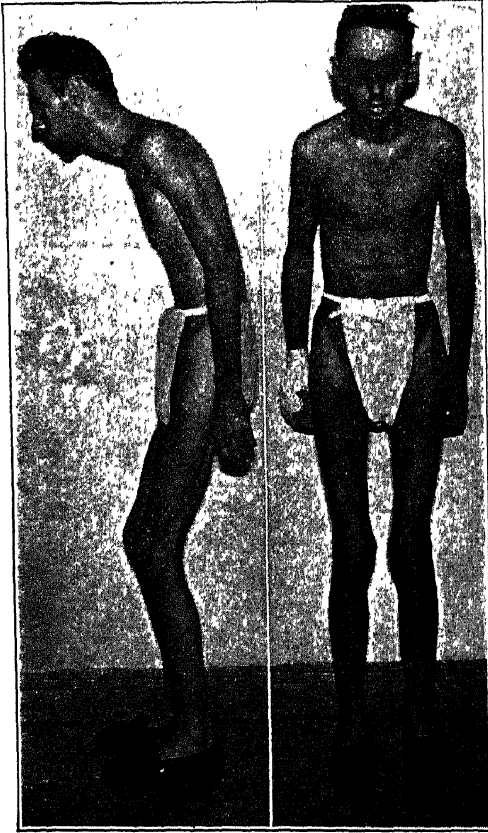


Fig. 44-A—Before treatment.



Fig. 44-B—After treatment.

(Smith-Petersen, M. N., Lawson, C. B. and Aufranc, O. E.:  
J. Bone & Joint Surg. 27: 1 (Jan.) 1945.)

cases are presented and all have yielded satisfactory results (osteotomy of the spine).

#### Lateral Dislocation of the Patella

McCarroll and Schwartzmann<sup>21</sup> have contributed another operative procedure for recurrent lateral dislocation of the patella. It consists briefly of transferring the tibial tubercle to restore a correct line of pull for the extensors of the knee

#### Analysis of One Hundred Consecutive Arthrotomies for Traumatic Internal Derangement of the Knee Joint

An analysis has been given of 100 consecutive cases of arthrotomies performed on European miners working underground in the Witwatersrand Gold Mines. Pain at the anteromedial joint line was found to be of considerable

diagnostic significance. Absence of such pain counterindicated an arthrotomy for a meniscal lesion. Locking was found frequently but not always due to the meniscal lesion (a stub of the anterior cruciate ligament was the cause of locking in one case). Meniscal damage may exist in the absence of wasting.

the ninety-seven torn menisci, forty-nine were of the bucket handle type. The end results of the treatment were given a disability assessment averaging 1.6 per cent. The findings in their investigation led the authors to favor early and total meniscectomy once an incontrovertible diagnosis had been reached.

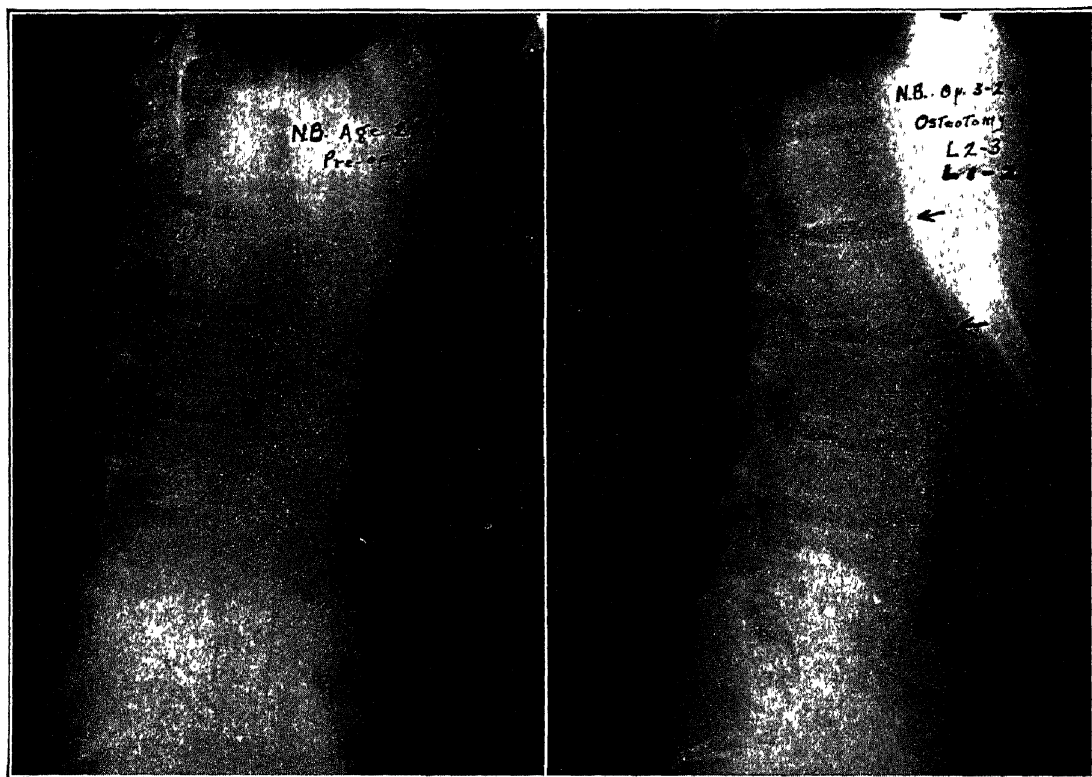


Fig. 44-C—Before treatment.

Fig. 44-D—After osteotomy.

(Smith-Petersen, M. N., Lawson, C. B. and Aufranc, O. E.:  
J. Bone & Joint Surg. 27: 1 (Jan.) 1945.)

Pain at the deranged meniscus site was found frequently on abduction or adduction of tibia on femur. However, it is not always present.

The analysis of the operative findings was as follows: In four cases, no meniscal lesion was discovered at time of operation. In eighty-two cases, tears of the medial meniscus were found. In nine cases, tears of the lateral meniscus were seen. There were double tears in three cases and a discoid meniscus in two. Of

In addition to the conclusions from the analysis of a large series of cases (see the above), the authors call attention to two signs which are not clearly mentioned in English literature, namely, (1) the hot spot of Fouché and (2) the crushing sign. The hot spot of Fouché is apparently pain and tenderness due to traumatic lesions of the cartilage of the medial facet of the patella. The crushing sign is pain at the site of the deranged meniscus on abduction or adduc-

tion of tibia on the femur (adduction—internal meniscus; abduction—external meniscus). The internal rotation of the tibia, a maneuver first described by

joint line, the right hand firmly grasping the patient's right foot, using it as a lever, internally rotating the tibia on the femur. The motion is carried through as a complete circumduction, movement starting with the knee fully flexed and ending with it slightly flexed. The menisci move with the tibia and, with this maneu-

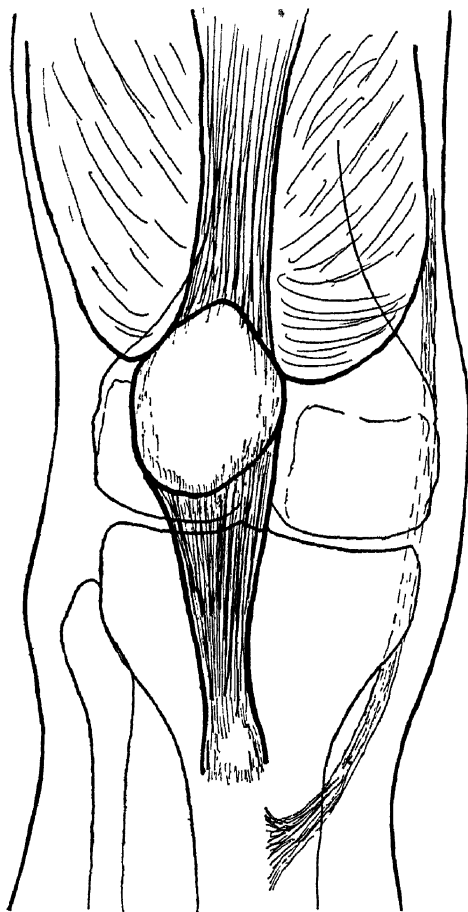


Fig. 45-A—Diagrammatic sketch of the knee, showing the usual relationship of the patella, patellar tendon, and tibial tubercle, with the knee extended in a congenital recurrent dislocation of the patella. Note that the patella lies over the lateral condyle, rather than in the groove between the two condyles. Also shown is the normal insertion for the tendon of the semitendinosus muscle. (McCarroll, H. R. and Schwartzmann, J. R.: *J. Bone & Joint Surg.* 27: 448 (July) 1945.)

Fouche, is also considered of great value in diagnosis. The test is carried out on the right knee as follows: The patient is placed flat on the back on a couch with hip and knee fully flexed. The fingers of the left hand of the examining surgeon are held on the anteromedial

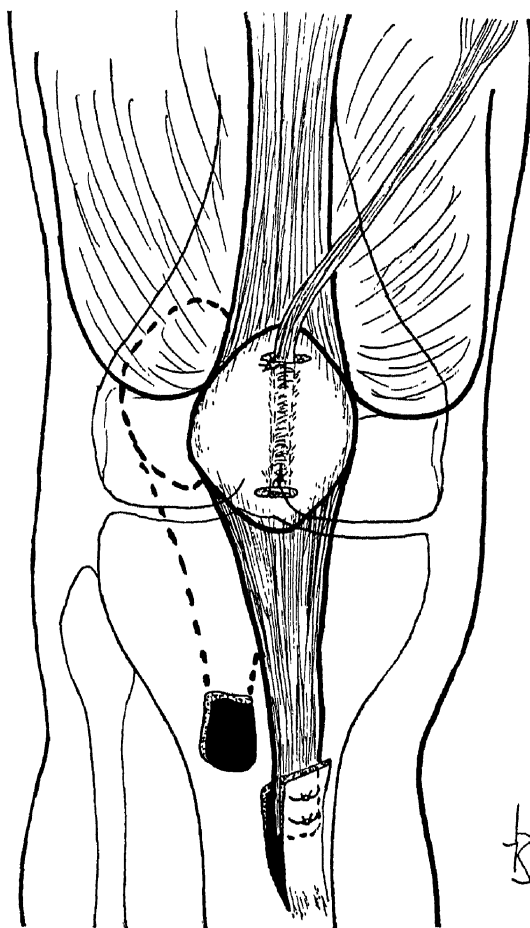


Fig. 45-B—Diagrammatic sketch, showing the same knee seen in Fig. 45-A, following operation. The tibial tubercle has been transplanted medially and inferiorly on the shaft of the tibia, and the insertion of the semitendinosus tendon has been transplanted into the patella. Note that the patella is now fixed in its normal midline resting position. (McCarroll, H. R. and Schwartzmann, J. R.: *J. Bone & Joint Surg.* 27: 448 (July) 1945.)

ver, the posterior end of the medial meniscus is nipped between the femoral and tibial condyles, the tendency being for the femoral condyle to force the menis-

cus towards the center of the joint. It may move a small distance and then slip back, producing an audible and palpable thud. With practice, the normal thud is recognized and the other sounds are distinguished. The sound a torn meniscus may make depends upon the type of tear. A grossly torn and frayed meniscus may produce a crunch or a squelch. A narrow bucket handle strip of cartilage gives a high-pitched click. Multiple splits in the posterior part of the meniscus produce a succession of clicks.

This is too extensive to brief and it would be well worth while for anyone interested in meniscus injuries to review the entire article.<sup>22</sup>

### Difficult Fractures of the Neck of the Femur Treated With the Stud Bolt Screw

The author<sup>23</sup> has operated upon eighty patients, using the stud bolt screw, since July, 1940. The results have been excellent. Breaking or slipping of the screw has not been observed in any case. A

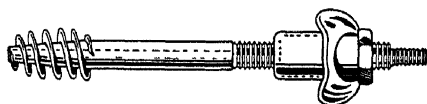


Fig. 46—The screw assembled. (Godoy-Moreira, F. E.: *J. Bone & Joint Surg.* 27: 595 (Oct.) 1945.)

number of difficult cases are reported in this article for the purpose of illustrating the efficiency of the screw. Fig. 46 shows the mechanical construction of the screw, the guide pins and other instruments used in its insertion. Figs. 47A, 47B, 47C, 48A, 48B, and 48C demonstrate the successful use of this particular apparatus. The stud bolt screw differs from the Smith-Petersen nail so commonly used in this country, mainly in that it is possible to impact the fracture thoroughly with the aid of the bolt on the trochanter end of the

screw. MacAusland and Virgin, in the *Annals of Surgery*,<sup>10</sup> presented a continuous traction screw with principles somewhat similar to the stud bolt screw. Threaded steel wires, popularized by Moore, Compere, and others, have similar fundamental principles. The results of Godoy-Moreira are excellent.

### Congenital Absence of the Radius

Starr<sup>24</sup> suggests a three-stage procedure, namely, skeletal traction, an ulnar osteotomy and fibular transplant. Figs. 49A, 49B, and 50 are illustrative. Congenital absence of the radius is the most common anomaly of the forearm. Various procedures for the replacement of the radius have been introduced in the past several decades. These include splitting the lower end of the ulna and transferring the radial half over to the navicular bone, whole tibial or whole fibular transplants running from the ulna to the first carpal row, osteotomy of the lower end of the ulna, and others. Practically all of these procedures have been failures in view of the fact that the substitute for the radius has not maintained the growth rate of the ulna. The end result in most of these cases has been a recurrence of the radial club hand and the loss of supination and pronation as well as restricted motion at the wrist, and frequently in the fingers. Starr has presented a technic which seems to eliminate these difficulties. A longer follow-up would be necessary to evaluate the technic properly.

### Surgical Obliteration of Bone Cavities Following Traumatic Osteomyelitis

The authors<sup>25</sup> have suggested the following plan for the obliteration of bone cavities following traumatic osteomyelitis: (1) Adequate sequestrectomy; (2)

application of a split skin graft; (3) excision of the initial skin graft; obliteration of the cavity with bone chips and transfer of full thickness skin graft. Twenty-three cases are reported. In all but two, the wounds were entirely healed. Bone sepsis was eradicated in all cases of the series; and, in all, the defects have been eliminated. There occurred no sequestration of the chips and no evidence of osteomyelitis following their insertion.

In the editor's opinion, possible application of this technic to large osteo-

myelitis cavities secondary to hematogenous osteomyelitis might well be kept in mind.

### Osteomyelitis of the Skull

The authors<sup>26</sup> briefly but thoroughly discuss osteomyelitis of the skull. There has been marked improvement in results since the advent of penicillin and the replacement of the large skull defect (secondary to the osteomyelitis) by a tantalum plate. Figs. 51, 52, 53, 54*A*, and 54*B* are illustrative of the defect, the tantalum replacement and the post-



Fig 47—*A*, Case 2 August 20, 1941 *B*, October 7, 1943 *C*, October 7, 1943  
(Godoy-Moreira, F. E. : J. Bone & Joint Surg. 27 : 595 (Oct.) 1945.)



Fig 48-A—Case 3. Sept 3, 1941 Fig. 48-B—March 27, 1944  
(Godoy-Moreira, F. E. : J. Bone & Joint Surg. 27 : 595 (Oct.) 1945.)

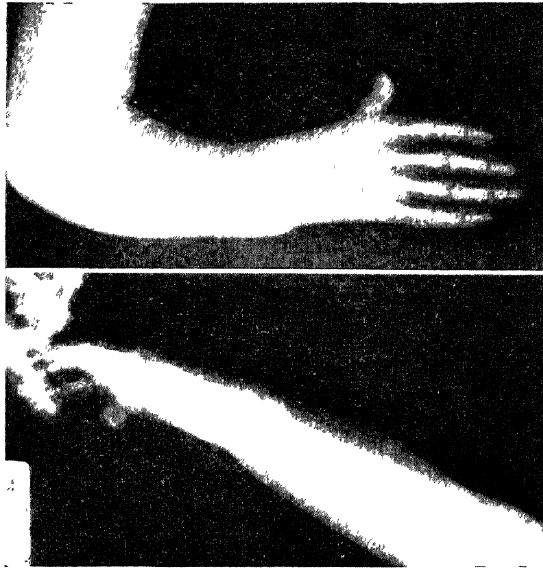


Fig. 49-A—Roentgenograms one and a half years after fibular transplant. Note patient's epiphysis in transplant. (Starr, D. E. J. Bone & Joint Surg. 27: 572 (Oct.) 1945.)



Fig. 49-B—Photograph one and a half years after correction. (Starr, D. E. J. Bone & Joint Surg. 27: 572 (Oct.) 1945.)

operative clinical picture. Their conclusions may be summarized as follows: Osteomyelitis of the frontal bone is a serious surgical disease because of the difficulty of limiting the spread of the infection. The organism is *Staphylococcus albus* or *aureus* in most instances. Penicillin is an excellent bacteriostatic agent in these cases, making it possible to bring the infectious process under

### Rapid Development of Bone Changes in Patients With Syringomyelia as Observed Roentgenologically

Pendergrass *et al.*<sup>27</sup> have had under observation a patient with syringomyelia. Fig. 55 is a roentgenogram of the left shoulder girdle (Feb. 17, 1942), showing a normal shoulder. The patient at that time complained of what was thought to be subdeltoid bursitis.

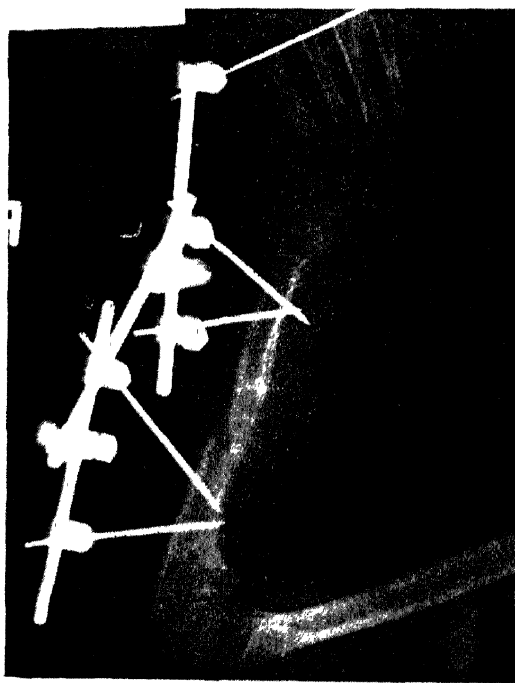


Fig. 50—External fixation following osteotomy. (Starr, D. E.: *J. Bone & Joint Surg.* 27: 572 (Oct.) 1945.)

control early and permitting surgical removal of the diseased bone. (Penicillin is not substituted for surgery.) The correction of the postoperative defect (preferably three months after the primary operation for osteomyelitis) with the aid of a tantalum plate (0.015 inch thick) has proven very satisfactory in the restoration of normal contour. The metal can be molded and pounded in the cold state and made to cover the defect smoothly and solidly. It causes no discomfort to the patient.

Figs. 56 and 57, taken on March 24, 1942, show complete destruction of the head of the humerus, considerable bony debris in the joint and moderate destruction of the glenoid fossa and the scapula. At this time the patient had a swollen aching shoulder that dislocated forward and backward and could be reduced painlessly. A neurological study revealed rather characteristic findings of syringomyelia. The author raises the pertinent questions namely: (1) What is known about the rapidity of the

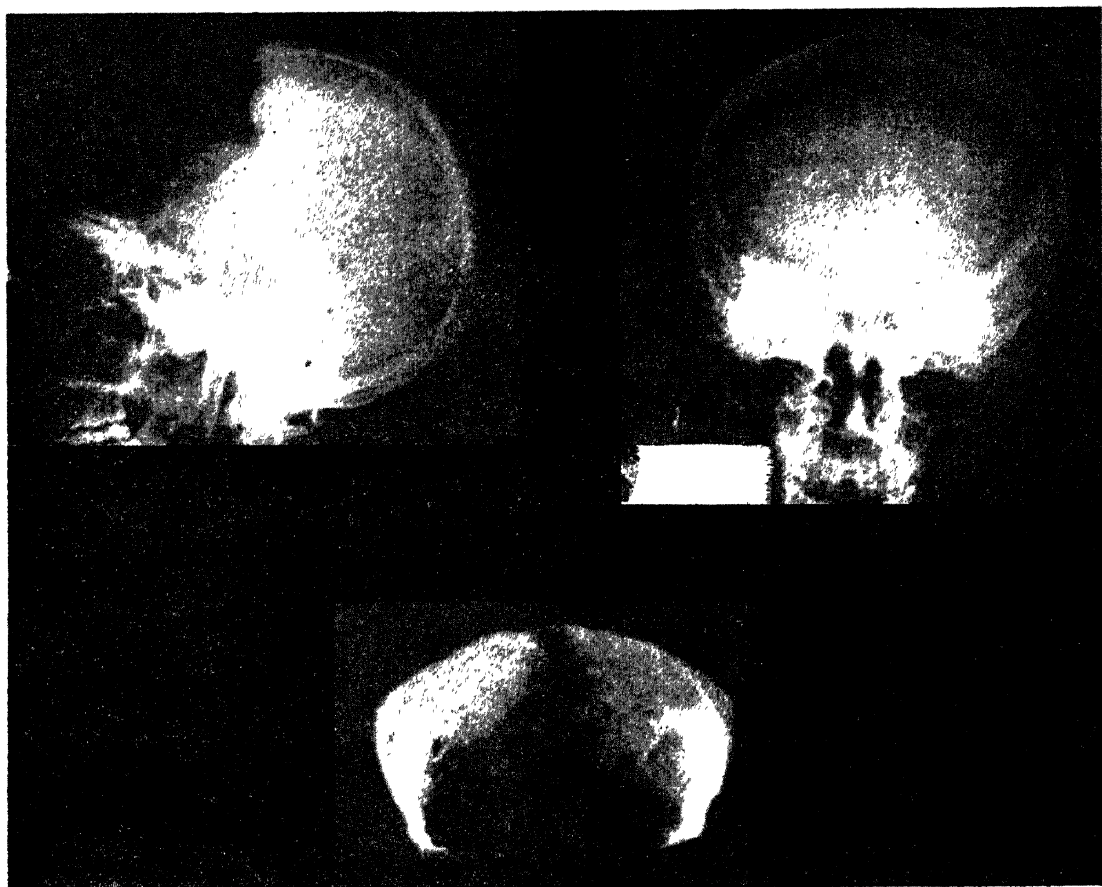


Fig. 51—Postoperative x-ray pictures of the anteroposterior and lateral views, showing the frontal skull defect and the excised bone fragments (November 18, 1943). (Schnitker, M. D. and McCarthy, M. D.: Surgery 18: 94 (July) 1945.)

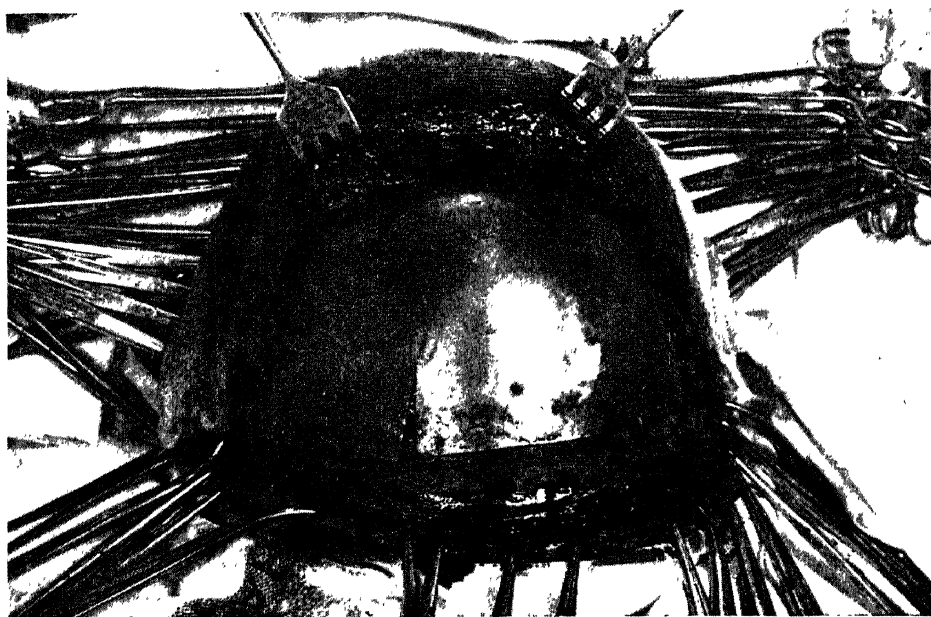


Fig. 52—G. M. The tantalum plate anchored in position by means of tantalum wire (May 1, 1944). Note perforation referred to in text. (Schnitker, M. D. and McCarthy, M. D.: Surgery 18: 94 (July) 1945.)



changes in a neuropathic joint? (2) How do the pathologic changes progress to a certain point and then become remarkably stationary? (Fig. 58); (3) What is the medicolegal status of such

a case? The answers to these are partly covered in the following: "Some of the literature reviewed reveals that severe trauma or minor injury often repeated may result in the rapid development of

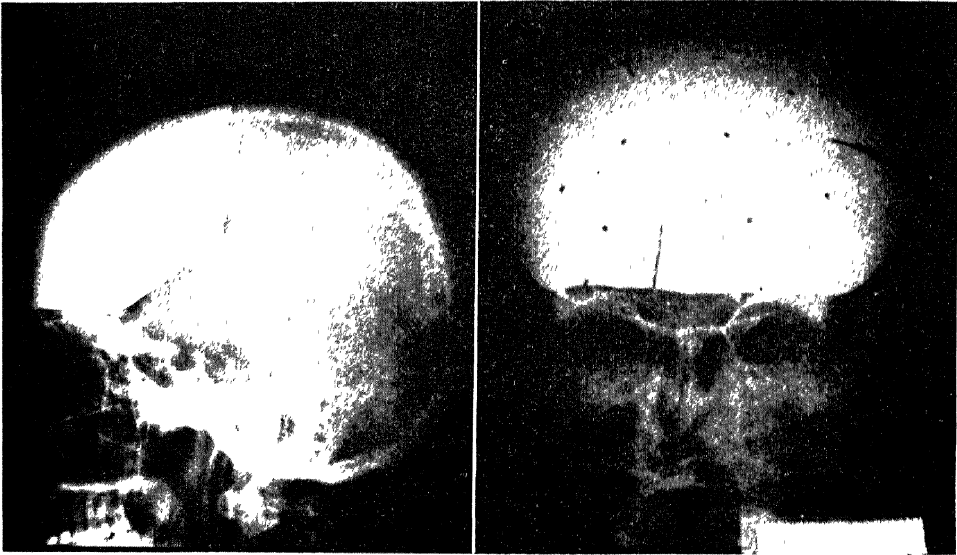


Fig. 53—G M. Postoperative x-ray anteroposterior and lateral views, May 17, 1944, showing tantalum plate firmly fixed in position. (Schnitker, M. D. and McCarthy, M. D.: *Surgery* 18: 94 (July) 1945.)



A

B

Fig. 54—A and B—G M. Anteroposterior and lateral photographs taken May 2, 1944, after insertion of tantalum plate and showing contour of frontal skull; facial scars to be corrected by plastic procedure. (Schnitker, M. D. and McCarthy, M. D.: *Surgery* 18: 94 (July) 1945.)

neuropathies. Reports are available suggesting that injuries occurring prior to the development of neuropathic joints may have a medicolegal compensatory importance."

### **Intervertebral Spine Fusion With Removal of the Herniated Intervertebral Disk**

Ovens and Williams<sup>28</sup> present a preliminary report of a new method of spine

reported. It is entirely too early to draw conclusions concerning the type of fusion that will occur following this type of graft.

### **Treatment of Skeletal Metastasis Secondary to Carcinoma of the Prostate**

Peck<sup>29</sup> emphasizes the frequency of low back pain produced by skeletal metastasis from prostatic carcinoma. Metas-



Fig. 55—Roentgenogram of left shoulder girdle, February 17, 1942, showing nothing abnormal, no roentgen evidence of bursitis. (Pendergrass, E. P., Gannon, G. D. and Powell, J. H. *Radiology* 45: 139 (Aug.) 1945)

fusion following removal of the intervertebral disk. Briefly, the method amounts to a removal of the disk, curettement of the cartilaginous plates and the insertion of an intervertebral graft. The graft consists of a spinous process and small fragments of bone rongeuired away when the lamina was removed. Two cases are

tases from this type of carcinoma, according to the author, are predominantly to pelvis, sacrum, and lumbar spine. Any man over fifty complaining of low back pain should have a rectal examination as well as a routine orthopedic examination. X-rays of the spine and pelvis plus alkaline and acid phosphatase determina-



Fig. 56.



Fig. 57.

Figs. 56 and 57—Roentgenograms in internal (Fig. 56) and external (Fig. 57) rotation, made March 24, 1942, approximately five weeks after the original examination (Fig. 55). The head of the humerus is completely destroyed and there is considerable bony debris in the joint. The glenoid fossa of the scapula is also involved. Many studies have been made of this shoulder over a two-year period and the bone destruction has increased only slightly. (Pendergrass, E. P., Gannon, G. D. and Powell, J. H.: *Radiology* 45: 139 (Aug.) 1945.)

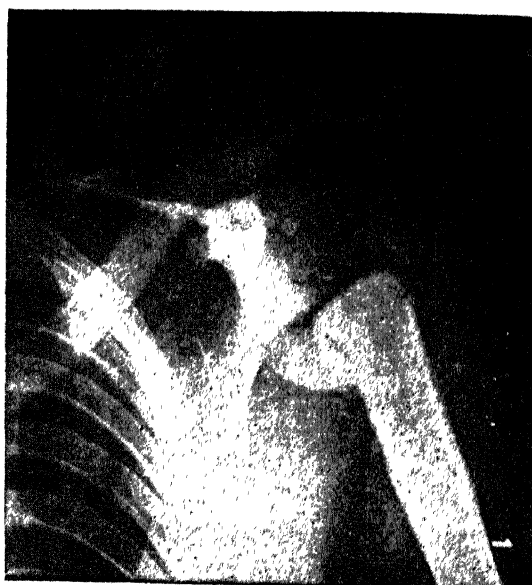


Fig. 58—Roentgenogram of left shoulder, July 19, 1943, seventeen months after original examination (Fig. 55); bone destruction in the scapula and humerus is increased only slightly. (Pendergrass, E. P., Gannon, G. D. and Powell, J. H.: *Radiology* 45: 139 (Aug.) 1945.)

tions aid in the diagnosis in suspected cases. *Orchiectomy* and *estrogen* are emphasized as means of relieving pain.

### Tuberculosis of the Spine

"Recovery from tuberculosis of the spine, following extension fusion, may be so complete as to cause a watchful Pathology Service to upbraid an active

teria as diagnostic and proceeded with a fusion to cover the involved area, in the case reported. Figs. 59*A*, 59*B*, and 59*C* illustrate the probable tuberculosis of the seventh thoracic intervertebral joint accompanied by paravertebral abscess. The spine fusion to which he refers was performed in 1930. The patient died in 1944. The autopsy, Figs.

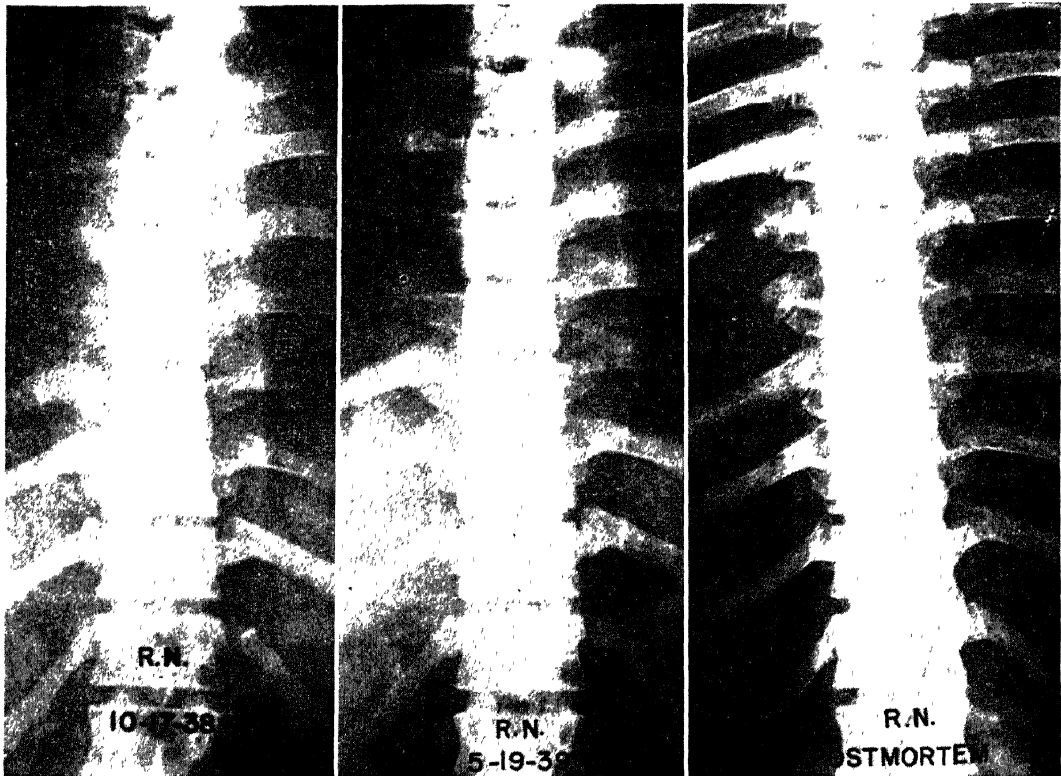


Fig 59—*A*, R.N. Paravertebral shadow of third to twelfth thoracic vertebrae with slight narrowing of the disk of the seventh thoracic vertebra. *B*, Shadow of the paravertebral abscess has decreased in the seven months following spine fusion. *C*, X-ray just before autopsy. Five years since *A* (Bosworth, D. M. J Bone & Joint Surg 27: 491 (July) 1945)

Orthopedic Service for having performed spine fusion on an assumed diagnosis of tuberculosis of the spine, some years before the patient's death." The presence of a paravertebral abscess in the thoracic region is the earliest criterion for the diagnosis of tuberculosis of the spine, far antedating bony or interspace changes. The author accepts such cri-

teria as diagnostic and the gross and the microscopic pathology as well as the excellent spine fusion.

This article is worth while presenting in that the author brings out the value of early fusion in tuberculosis. In this particular instance, spine fusion was performed early; in fact, so early that the subsequent autopsy findings questioned

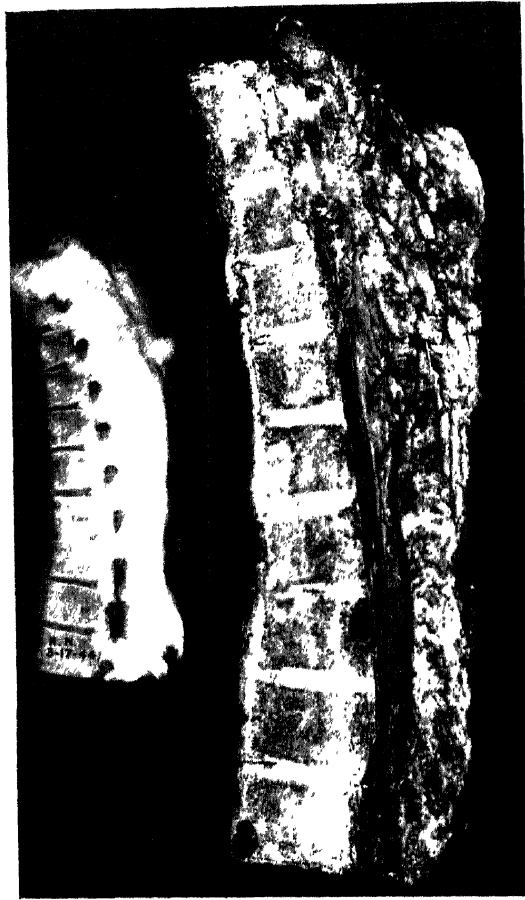


Fig. 60—Gross specimen of spine split showing slight narrowing of the disk of the seventh thoracic vertebra with apparent vacuolation of center. Roentgenogram shows some calcification of the disk of the seventh thoracic vertebra without gross involvement of the vertebrae elsewhere (Bosworth, D. M. : J. Bone & Joint Surg. 27 : 491 (July) 1945.)



Fig. 61—Photomicrograph showing concentric area composed of hyalinized connective tissue surrounded by loose connective tissue. No other such areas were found. This is a tiny residual for such massive previous involvement (Bosworth, D. M. : J. Bone & Joint Surg. 27 : 491 (July) 1945.)

the fact as to whether tuberculosis had previously existed<sup>30</sup>

### **Closed Manipulation for the Reduction of Fractures of the Neck of the Radius in Children**

The author<sup>31</sup> reports four cases of fractures of the neck of the radius in

is true if occupying an anterior position. The purpose of adducting the forearm on the arm is to reopen the radial humeral joint space. Figs 62*A* and 62*B* are illustrative.

The value of this paper is to stress the fact that conservative measures should be employed in fractures of the

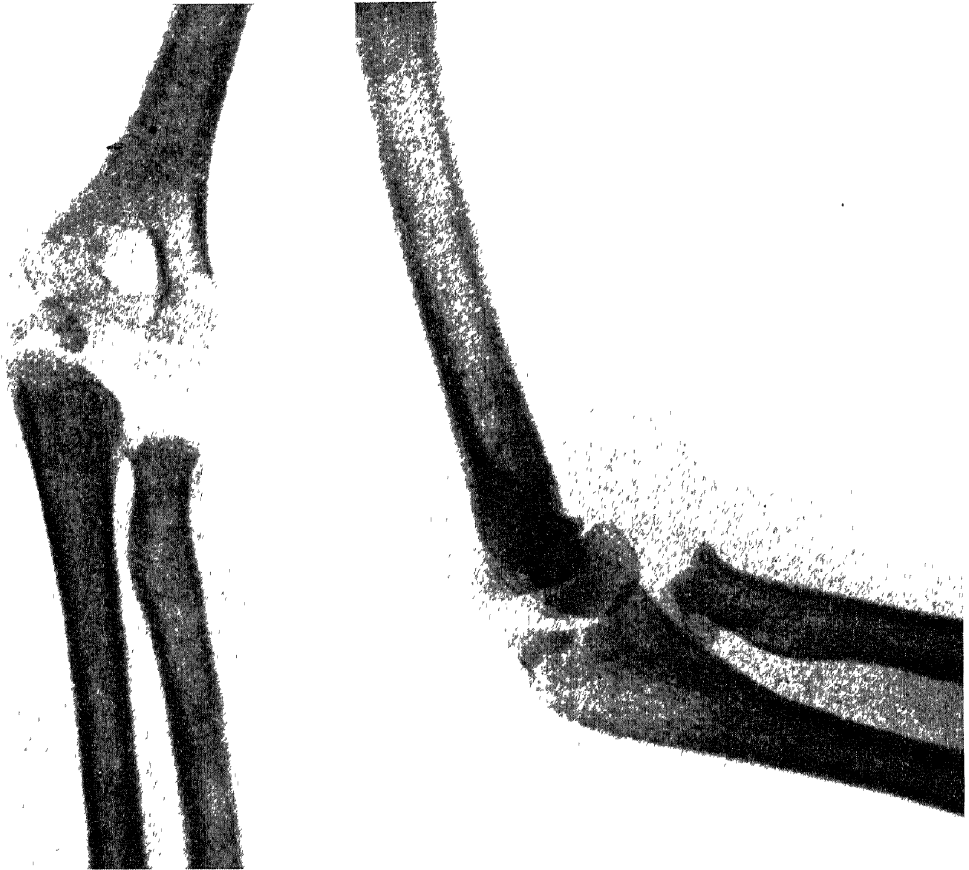


Fig 62-A—Case 2 Fracture of the neck of the radius before reduction. (Goldenberg, R. R. . J Bone & Joint Surg 27:267 (April) 1945 )

which the reduction was successfully acquired by the so-called Patterson maneuver. The maneuver is briefly described as follows: The elbow is extended, forearm supinated. The forearm is then adducted on the arm, reversing the normal carrying angle. If the fragment, including the radial head and neck, is displaced posteriorly, it is pushed forward by digital pressure. The same

radial neck and head in children. The results here are excellent.

### **An Operation for the Correction of Locking of the Proximal Interphalangeal Joint of Finger in Hyperextension**

Figs. 63 and 64 are illustrative of this deformity. Hyperextension of this particular joint and other joints is not

an uncommon finding in traumatology. This particular case justifies a review in that the pathology has been clearly demonstrated and the method for repair has been well outlined. The method is applicable to hyperextension of other joints

flexor sublinus digitorum tendon was avulsed. The volar ligament had been pulled away from the proximal phalanx and was contracted. The middle phalanx could be luxated on the proximal phalanx and this accounted for the locking. Repair consisted of resuturing the volar ligament to the proximal phalanx and a repair of the lateral capsule in such manner as to reinforce the volar ligament. A four-month follow-up revealed



Fig. 62-B—Fracture of the radius after reduction (Goldenberg, R. R.: *J. Bone & Joint Surg* 27: 267 (April) 1945.)

with this sort of pathology. The author reports that the patient was unable to control the plane properly due to his inability to grasp the throttle with his right hand due to the hyperextension locking of the proximal interphalangeal joint of the fifth finger. At the time of operation the volar capsule was found to be absent. The medial attachment of the

BEFORE OPERATION

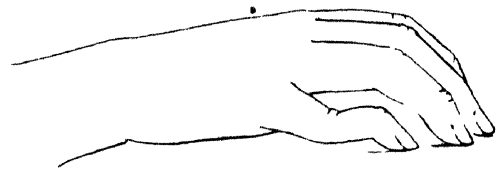


Fig. 63—Drawing showing the fifth finger locked at the proximal interphalangeal joint. (Bate, J. T.: *J. Bone & Joint Surg* 27: 142 (Jan.) 1945.)

a successful correction of the recurrent dislocation. Figs. 65, 66, 67, 68 and 69 outline the technic of the operation.<sup>32</sup>

### Costoclavicular Compression of the Brachial Plexus and Subclavian Vessels

The author<sup>33</sup> presents a case of compression of the subclavian vessels and the brachial plexus between the clavicle and the first rib. Figs. 70 and 71 are radiographs illustrating the venography and clearly demonstrating the subclavian compression. Figs. 72 and 73 illustrate the sensory loss before and after surgery. At the time of suppression, the artery and the plexus were very superficial and pushed forward by the first rib. They were bound to the rib and back of the clavicle by dense inflammatory fibrous tissue, rough and reddened as if subjected to repeated trauma. The artery was small and grooved transversely as if it had just been released from the grip of an intestinal clamp. A



Fig. 64—Roentgenogram showing the position in which locking occurred (Bate, J. T. J. Bone & Joint Surg. 27: 142 (Jan.) 1945.)

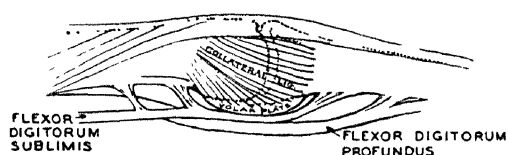


Fig. 65—Diagrammatic sketch showing the anatomy of the proximal interphalangeal joint of the finger. (Bate, J. T.: J. Bone & Joint Surg. 27: 142 (Jan.) 1945.)

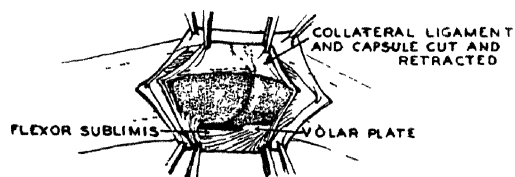


Fig. 67—Drawing of the tear on the volar portion of the capsule. (Bate, J. T.: J. Bone & Joint Surg. 27: 142 (Jan.) 1945.)

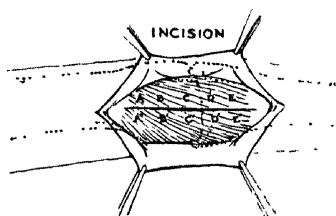


Fig. 66—Sketch showing the line of incision through the lateral part of the capsule of the proximal interphalangeal joint. The lettering helps to illustrate the method of repair. (Bate, J. T.: J. Bone & Joint Surg. 27: 142 (Jan.) 1945.)

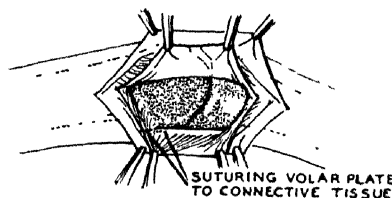


Fig. 68—Drawing showing the repair of the volar plate of the capsule. (Bate, J. T.: J. Bone & Joint Surg. 27: 142 (Jan.) 1945.)



finger could hardly be introduced into the narrow space between the rib and clavicle in front of the artery and lower trunk and it was tightly nipped when the patient was asked to brace her shoulders back, a movement which com-

pressed the artery and nerves hard against the first rib. Three cm. of the first rib were excised, allowing the artery and lower trunk to fall back comfortably against the pleura. The writer believes that the mechanism (previously

AFTER OPERATION



Fig. 69—Sketch showing the final result of the operation. (Bate, J. T.: J. Bone & Joint Surg. 27: 142 (Jan.) 1945.)

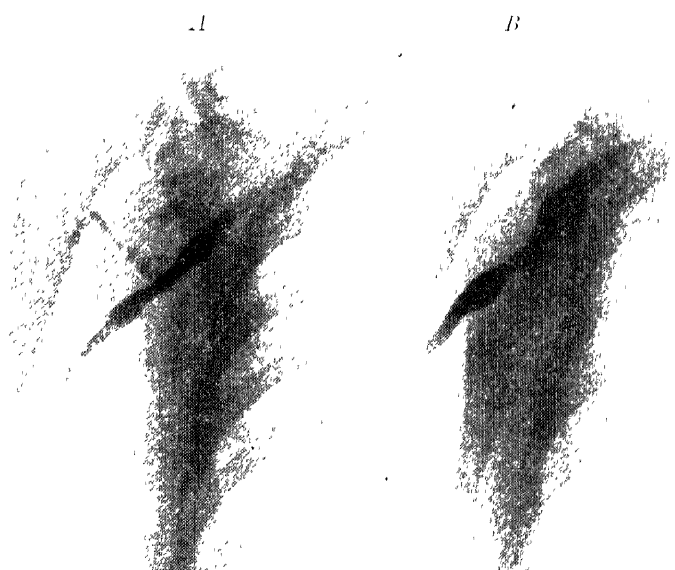


Fig. 70

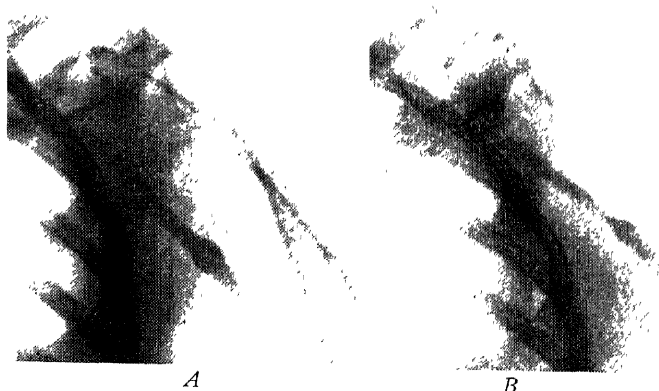


Fig. 71

Fig. 70—Venography in the right arm before operation. *A*, At rest; *B*, with shoulders braced back. Note venous distention in the upper axillary trunk in *B*. (LeVay, A. D.: Lancet 2: 165 (Aug. 11) 1945.)

Fig. 71—Venography in the left arm. *A*, At rest; *B*, with shoulders braced. The movement does not affect venous caliber. (LeVay, A. D.: Lancet 2: 165 (Aug. 11) 1945.)

described by Falconer and Weddell, 1943) is a common one and that its effect may be exaggerated by the division of the scalenus anterior. He stresses the value of venography as an aid in diagnosis.

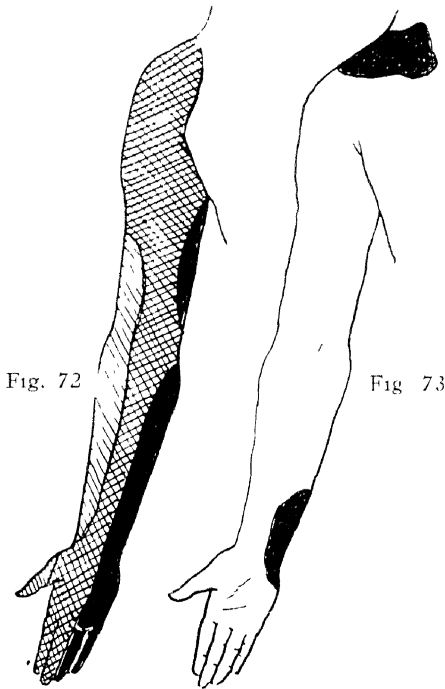


Fig. 72

Fig. 73

Fig 72—Sensory loss before operation. Loss is proportional to depth of shading (LeVay, A D Lancet 2: 165 (Aug 11) 1945)

Fig 73—Postoperative sensory chart. (LeVay, A D Lancet 2: 165 (Aug. 11) 1945.)

### Dual Plates for Internal Fixation in Nonunion of Fractures

Key<sup>34</sup> recommends the employment of dual metallic plates as a means of obtaining the best fixation in cases of pseudoarthrosis of long bones. He frequently supplements the two plates with free tibial grafts (Phemister). Figs. 74 and 75 are illustrative.

The employment of dual plates entails considerably more surgery than the use of a single plate or the heavy onlay graft, or external bar pin fixation. (Stader, Anderson, etc.). Possible injury to blood supply as well as introduction of extra

metallic materials has to be considered. The possibility of refracture through the numerous drill holes adjacent to the already weakened area (pseudoarthrosis) is of considerable importance. Boyd, in the *Journal of Bone and Joint Surgery* in 1941, introduced the use of the dual bone grafts for congenital pseudoarthrosis. This procedure would seem to be

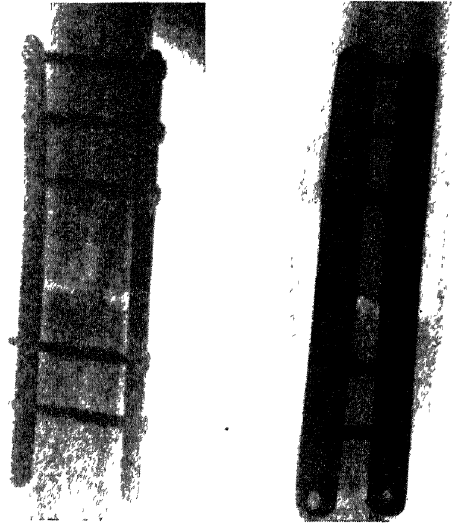


Fig 74—Old fracture of the femur, fixed by dual plates, supplemented by barrel-stave grafts. (Key, J. A. J Bone & Joint Surg. 27: 634 (Oct) 1945.)

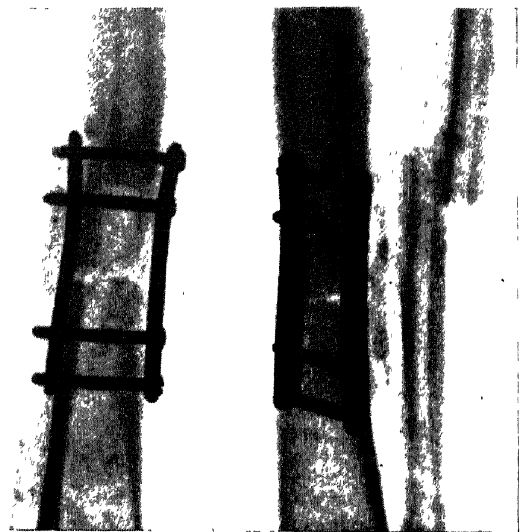


Fig 75—Old fracture of the tibia, fixed by dual plates, supplemented by iliac grafts. (Key, J. A.: J. Bone & Joint Surg. 27: 634 (Oct.) 1945.)

a better physiological approach than the method suggested by Key.

It has been presented in this review merely because it shows the general trend towards internal mechanical fixation of fractures.

### Disarticulation of the Innominate Bone for Malignant Tumors of the Pelvic Parietes and Upper Thigh

"Sugarbaker and Ackerman<sup>35</sup> state that ninety-nine patients (collected by Leighton and the authors) have been operated on for tumors of the bone or soft parts in the region of the upper femur or pelvis. Although an overall mortality of 28 per cent exists, that of the first forty-year period was 56 per cent. During the past ten years, the mortality has dropped to 14 per cent. This drop has been largely due to improvement in the treatment of shock, which has been the primary complication of this operation. Of forty-five patients surviving operation and followed from one to five years or more, twenty-one remained clinically well and twenty-four died. The deformity, although considerable, is borne gracefully by these patients. Far too few patients have received the benefit of radical operation. Advantages of wide resection have not been sufficiently exploited, particularly as regards partial or incomplete removal of the innominate bone when that bone itself represents the site of the tumor. With more adequate control of the mortality, patients will be selected less on the basis of age and more on the basis of the pathology of the tumor. Consideration of these factors will influence the prognosis in sarcoma of the upper thigh and pelvic parietes."

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## PLASTIC AND RECONSTRUCTIVE SURGERY

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## PLASTIC SURGERY

## Plastic Closure of Skull Defect

Harris and Woodhall<sup>1</sup> describe implant of tantalum plate beneath tube graft transplant for secondary repair of skull defect caused by war injury; a case report is included. The missile produced a compound, comminuted, de-

Healing of the pedicle graft progressed normally and a satisfactory cosmetic result was obtained.

The authors stress the value of utilizing tubed pedicle grafts in conjunction with tantalum plates to offer prompt coverage for cranial defects and therewith frustrate many troublesome sequels of brain injuries.

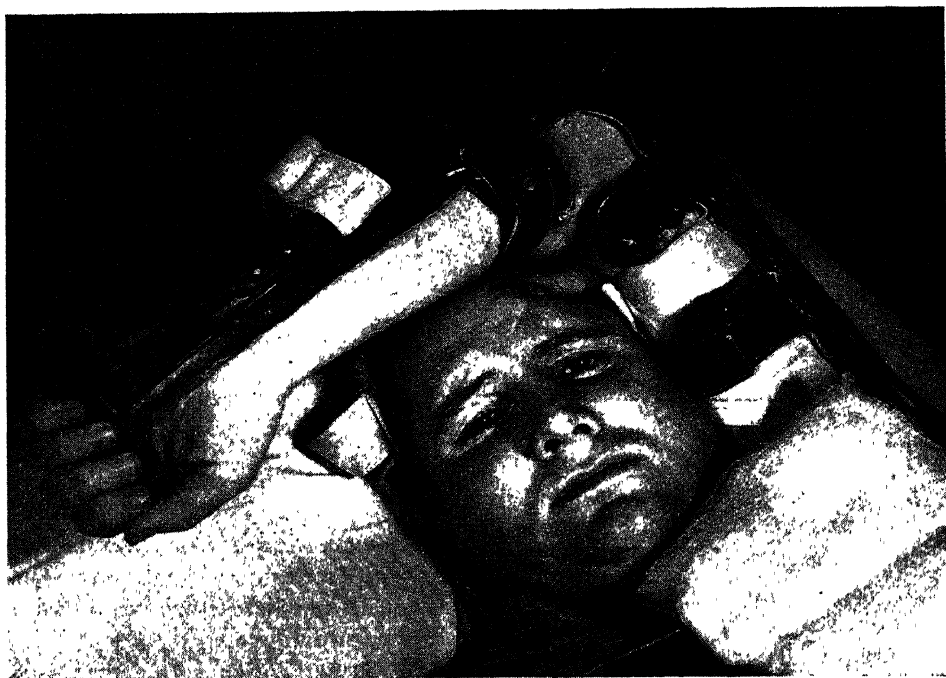


Fig. 1—Showing the first stage of transference of graft to scalp defect. (Harris, M. H. and Woodhall, B.: *Surgery* 17: 422 (March) 1945.)

pressed fracture. Patient had a stormy recovery. After several surgical interventions, including implantation of a tantalum plate, the plate healed marginally only and the remaining exposed part was covered by a double pedicled tube graft which had come from the upper arm (Fig. 1).

## Complete Avulsion of the Scalp

Eisenstodt<sup>2</sup> reviews literature on avulsion of the scalp and outlines the respective treatment when (1) the pericranium is intact or only slightly injured, and (2) when a more extensive loss of the pericranium exists and says that with the advent of the dermatome, coverage

of large defects caused by scalp avulsion is no longer a problem. One case is reported.

### Plastic Surgery of Nasal Fractures

Lamont's<sup>3</sup> paper deals primarily with deformities resulting from unreduced fractures. Advises thorough examination to establish diagnosis of fracture. He evaluates deformities of the septum, the tip, the bridge, etc., and gives briefly the method of their correction and also the correction of deformities that require addition of cartilage. He points out that unless reduced, fractured noses secondarily will need to be reconstructed physiologically as well as cosmetically. He advocates the use of neocartilage for such reconstruction and feels that its use has proved a valuable adjunct in repairing nasal depressions. The need of careful preoperative study to gain desired result is mandatory.

### Secondary Cleft Lip and Nasal Deformities—Repair of

Lamont<sup>4</sup> states that even with adequate initial surgery, secondary repair should be anticipated of the nasal deformity as well as of the lip. A reasonable reconstruction may be expected unless the lip is grossly too long or too tight.

He points out that considerate surgery, time, and later orthodontia, can do much to approximate even wide alveolar clefts, and that the damage to the maxilla from forceful wiring often results in irreparable malformations and loss of teeth. Even with double hare lip, especially with prominent or floating premaxilla, reasonable occlusions can result; sacrificing the premaxillary at the time of primary closure is of very unhappy consequences, a short, tight, or morbidly retruded upper lip will be the result.

The author points out that the prolabium is part of the lip, that primary repair must be carried out with utmost caution, the error being almost always in doing too much.

Reconstruction of secondary deformities call for preoperative study with casts

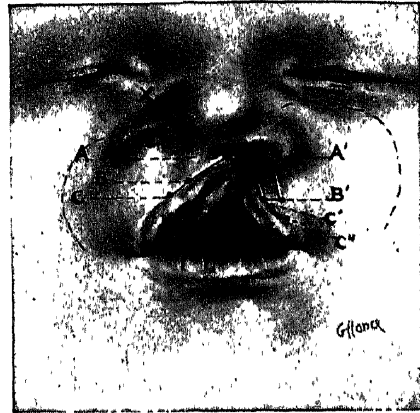


Fig. 2—The lines  $A-B-C$  and  $A'-B'-C'$  are lightly incised with a knife. The incision is carried upward from  $C'$  on the mucocutaneous junction to separate the vermillion from the skin. This is also done at  $A$  to keep any vermillion out of the nostril floor. The circular dotted lines show the area which is to be undermined at the next step. (Brown, J. B. and McDowell, F.: Surg., Gynec. & Obst. 80: 12 (Jan.) 1945.)

and photographs of lips, the nose, and alveolus; if more than one surgical stage is planned, Lamont operates on the nose first, correcting or replacing its-deformed or misplaced components and using cartilage, if needed, from the patient's nose or necrocartilage.

Lips that offer sufficient tissues are reformed as naturally as possible. In selected cases, an Abbe type of repair is resorted to. Occasionally, Lamont uses cartilage or dermal grafts in building up the upper lip. (Reviewer does not particularly advocate such approaches unless apparently unavoidable.)

Lamont states that secondary procedures may be carried out at any age; a complete rhinoplastic operation is not performed, as a rule, until the patient

has passed adolescence. The subject of speech training and prosthetics is touched.

### Single Cleft Lips—Simplified Design Repair

Brown and McDowell<sup>5</sup> review the Mirault technic described over one hundred years ago and also some modifications thereof described by Blair and Brown (1929). They point out that as

of rectangular flap (Fig. 2). Mobilization of lip and nose (Fig. 3). Relaxation (incisions) over anterior end of inferior turbinate; elevation of the skin of the nose (Fig. 4); excision of the cleft (Fig. 5). The preoperative and postoperative care of patients is explained, including feeding problems. A "Logan Bow" is used to relieve tension (Fig. 6). Closure of the lip and the use of scissors for trimming (Figs. 7, 8, 9, and 11).



Fig. 3—Incisions made in the buccal fornix on both sides and the soft tissues of the lip and cheek are taken loose from the bone, up almost to the lower border of the orbit on the cleft side. Less extensive mobilization may be necessary on the sound side, though it is sometimes necessary to elevate that nostril up out of the pyriform recess and to cut the base of the septum slightly before the normal ala and columella can be straightened. In any event, the mobilization is continued until the nose can be straightened and the two sides of the lip can be brought together without tension. (Brown, J. B. and McDowell, F.: *Surg., Gynec. & Obst.* 80: 12 (Jan.) 1945)

a result the lips in some cases come straight down from the nostril floor to the vermillion border, where normal lips should curve forward (as seen in profile). An artist's rendering of an ideal child's lip in profile is seen in Fig. 10. The authors' simplified design for repair of single cleft lip will overcome, or at least modify, to a major extent the lack of outward curvature at the lower lip border resulting from previously utilized technics.

A very detailed description of this operative technic is given, viz.: Outline

**Anesthesia** — Gives preference to ether vapor—supplementary with bilateral infraorbital block. Anesthetists are encouraged just to give enough to keep baby reasonably still and not enough to abolish cough reflex. Suction is used.

Intratracheal gas-ether anesthetic is used for patients old enough. Brown and McDowell say it is of major importance, at the primary operation, to obtain: symmetry of alar level, good alar direction toward the columella, a satisfactory nostril floor, a normal nostril curve (across the tip of the nose), a

straight columella, a natural contour as seen in profile, a vermillion without a notch. No part of the lip is to be grasped with forceps at any time during the repair unless it is to be discarded eventually. Primary healing is a prerequisite to gain a smooth repair.



Fig. 4—Undermining between the lining and skin of the nostril so that they will slide on each other when the nostril is rolled up into a tube. At times it is necessary to make the vertical cut shown just in front of the turbinate to allow complete rotation of the nostril. (Brown, J. B. and McDowell, F.: *Surg., Gynec. & Obst.* 80:12 (Jan.) 1945.)

The authors discuss an extensive variety of common deformities as seen in patients needing secondary repair.

### Fixity of Facial Expression Following Undermining of the Skin Over the Nose

Seltzer<sup>6</sup> reviews the evolution and the anatomy of the facial musculature including the external nose. He feels that during the usual rhinoplastic operation for removal of a bony hump, in the process of undermining the skin over the back of the nose, considerable injury is done to the deeper parts of the skin, and to the subcutaneous tissues, blood vessels, lymphatics, and nerves. He points out that in consequence of this disturbance the underlying nasal musculature is injured.

He states that following surgical removal of a nasal hump where undermining of the skin was practiced, a certain waxy immobility of the tissues about the nose has occurred. He feels that this local lack of facial mobility can be avoided by carrying out the entire operation for removal of a hump by elevating the periosteum (Reviewer—subperiosteally) instead of undermining only the skin.

### Care of the Injured External Ear

Every effort should be made to preserve all viable or questionably viable tissue in order to prevent conspicuous deformities and to help make reconstruction as nearly normal as possible.

The possibility of middle ear injury must be borne in mind, especially in the



Fig. 5—The lightly incised lines A-B-C and A'-B'-C' are cut completely through the lip with a stab blade, with care to keep knife exactly perpendicular to lip. All angles should be completely opened. The vermillion is inspected and any attached skin removed with a stab blade. The rectangular flap freed from A'-B'-C' must be loose enough to be rotated up 180 degrees into nostril floor. Dotted lines indicate area undermined. (Brown, J. B. and McDowell, F.: *Surg., Gynec. & Obst.* 80:12 (Jan.) 1945.)

event of skull fractures and appropriate measures of treatment should be instituted promptly.

Heat, cold, electricity, and noxious chemicals may produce intensive de-

struction, resulting in unavoidable deformities.

Gives technic of dressing of ear wound prior to grafting and recommends prompt application of free, thick split grafts to prevent avoidable contractures.

In cases of extensive destruction he advocates use of retroauricular skin flap, a cervical tubed pedicle flap or a combination of both and the addition of cartilaginous support as indicated.

Procedure consists of early and complete sequestrectomy, followed subsequently by application of split thickness grafts placed over the soft tissue wound and into the depths of the saucerized area so that the entire wound area may heal promptly. Bone does not, however, regenerate beneath these adhering split thickness grafts; the defects remain essentially the same and the split thickness grafts, being used only as temporary



Fig. 6—Partial clefts can have all of the problems of complete clefts including those of the nose. This patient has obtained a repair that is good except for the fact that the thickness of the ala runs vertically into the face instead of starting horizontally to proceed across toward the columella. (Brown, J. B. and McDowell, F.: *Surg., Gynec. & Obst.* 80:12 (Jan.) 1945.)

The use of prosthetics in exceptional cases, especially when the entire ear is destroyed, is advised.<sup>7</sup>

#### **Surgical Obliteration of Bone Cavities Following Traumatic Osteomyelitis**

Knight and Wood<sup>8</sup> describe technic involved in treating large bone cavities in tibia and femur, associated with loss of skin and soft tissues, and following infected compound fractures.

measures, are removed at the time of bone grafting and are (by these authors) replaced by full thickness grafts (flaps). They use the following three-stage program:

1. Thorough sequestrectomy and excision of scars.
2. Early split skin grafting, *i. e.*, as soon as a thin layer of granulating tissue has formed, and, finally, when the grafted area is completely epithelialized and the graft has become relatively stable.



3. The split thickness covering from the depth of the saucerized area is completely excised; the bone cavity is obliterated with autogenous bone chips, and the adjacent skin and soft tissues are undermined and made to slide so as to cover over the cavity filled with chips.

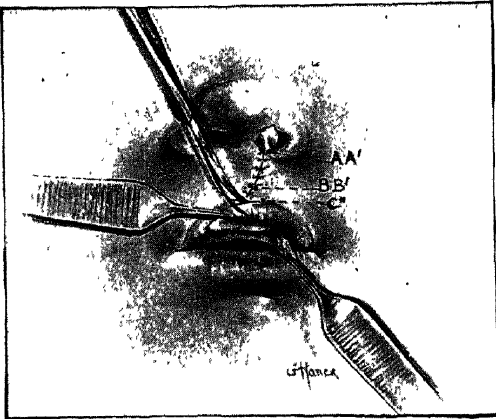


Fig 7—*A* and *A'* are approximated with a deep stitch of white silk or cotton or No. 000 catgut (knot on the mucosal side) and a surface suture of No. 000 black silk. *B* and *B'* are approximated with a fine deep white stitch and a black one on the surface. Intervening fine surface sutures are placed and an oblique cut is made in the vermillion flap from *C'*. For the incisions and trimming fine, very sharp scissors are most useful. (Brown, J. B. and McDowell, F.: Surg., Gynec. & Obst. 80: 12 (Jan.) 1945.)

Excessive tension must be avoided. The wound will heal best if the suture line does not directly overlie the chip-filled cavity. Some experience and good judgment are necessary in estimating the proportion of tissues that can be moved with safety.

### The Molded Bone Graft

The difficulty of carving ordinary bone grafts to shape and of immobilizing them in a simple manner has been overcome by the author's<sup>9</sup> technic of a molded bone graft. The use of this graft is somewhat limited; it appears not to be suitable where stress and strain are placed upon the graft. It is a simpler,

easier, and quicker method than the tantalum plate, which requires tedious fitting. The molded bone graft offers no barrier to blood circulation.

The graft is suited to contour restoration for defects about the face and head. The technic is simple and the cosmetic results are gratifying. The author feels that in selected cases it is superior to ordinary bone, cartilage, or dermal grafts.

In order to achieve satisfactory results, the operation must be planned and the site and extent of the loss must have been visualized (x-rays, plaster casts, etc.). Infections, osteomyelitis, etc., must have thoroughly healed and sufficient time elapsed before grafting is attempted and the skin covering must be in good



Fig. 8—*C* and *C'* are united and the vermillion flaps are interdigitated in a zigzag fashion, fitting them so that they lie naturally together without any pull or stretching. Suture is then continued on around the vermillion border and up the inside of the fornix. The little flap in the nostril is trimmed to fit with the one from the opposite side, and they are sutured together to form the floor. A few key mattress sutures are placed through the ala to unite the lining and covering (which were separated during the undermining). (Brown, J. B. and McDowell, F.: Surg., Gynec. & Obst. 80: 12 (Jan.) 1945.)

condition. The author gives the technic of taking impressions of the defect and of making the splint from a sheet of lead.

The recipient area is exposed prior to obtaining bone and grafting is not carried out if the wound becomes contam-

inated, since contamination spells failure. The old scar is used for the site of incision; the wound margins are undermined if necessary, and the bone is uncovered and freshened up; bleeding is arrested. Shavings of bone, 2 to 3 mm. thick, are secured from the iliac crest. The small

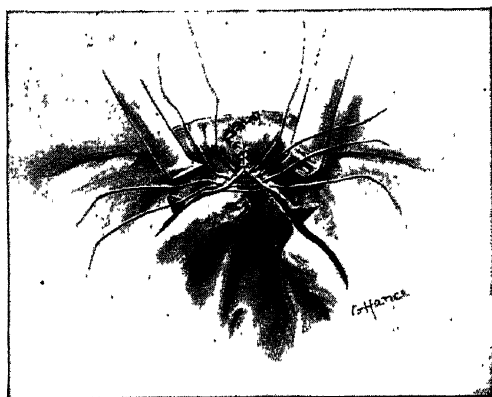


Fig. 9—The mucosal suturing is important and is done with fine interrupted stitches and careful trimming to fit the edges together. The upper corners are rounded somewhat, and the suturing is continued to pull some mucosa into the lip from either cheek. This advances the whole lip and thrusts it forward. If the superior edge of the mucosa is tight, vertical slits are made on either side and allowed to spread open. (Brown, J. B. and McDowell, F.: Surg., Gynec. & Obst. 80:12 (Jan.) 1945.)

pieces of bone are placed into a pre-formed pocket, and it is filled to overflow and the excess is pressed out by applying the molded lead splint and by applying gentle pressure before suturing the skin. A thin lining of dental modeling compound between the lead mold and the skin prevents the metal edges from cutting. When all is in order, a pressure bandage is carefully and evenly applied.

Postoperative care is described and photographs are presented.<sup>9</sup>

### Reconstructing Enlarged Breasts

Lamont<sup>10</sup> elaborates upon the embryology, the blood, lymph and nerve supplies, and the physiology of the breast,

and evaluates the end results of several procedures. He thinks that the anatomy and physiology of the breast, the type of deformity, and the pathology involved should be thoroughly understood in order to appraise the methods of approach. He briefly touched upon the evolution, the etiology, and mechanism of the deformities and gives a few hints for measurements.

He describes the surgical technic which he advocates and points out that the methods of the last two decades ignored contours, symmetry, and shape. He divides his surgical methods into three categories: one-stage mastopexy with *transposition* of the nipples; two-stage mastopexy with *transposition* of the nipples, and the two-stage mastopexy with *transplantation* of the nipples for mark-



Fig. 10—Normal profile of an infant showing the upper lip far in advance of the lower and the flexion crease in the upper lip with the forward thrust of its lower border. This gross contour of the upper lip and its relations to other features is visible and noticeable at a greater distance than are some of the finer details of the lip. (Brown, J. B. and McDowell, F.: Surg., Gynec. & Obst. 80:12 (Jan.) 1945.)

edly (pathologically—Reviser) enlarged breasts.

Lamont describes his surgical technic in detail with the pre- and postoperative treatment given. Diagrams and photographs are included in the article.<sup>10</sup>

### Two-Stage Mammaplasty in Relation to Blood Supply

The author<sup>11</sup> points out that unless adequate vascularization is preserved during mammaplasty necrosis of the skin and glandular structures will occur. He believes that the anatomy of the lateral thoracic artery as described by anatomists (and by him in the past) is not

the intradermic tissue itself. (Reviewer, *i. e.*, superficial to the layer of areolar tissue in which are found the blood vessels. Areolar glands must not be left behind.)

2. Adequate subcutaneous tissue must be included in the skin flaps to avoid injury to the main vascular branches located subcutaneously.



Fig. 11—Repair of wide single cleft by method described. The normal-appearing forward thrust of the lower portion of the lip was obtained by the use of a small flap in the lower one third of the lip with the mucosal suturing. (Brown, J. B. and McDowell, F.: *Surg., Gynec. & Obst.* 80: 12 (Jan.) 1945.)

entirely correct. He demonstrates in a series of diagrams his concept of breast circulation. He feels that thorough knowledge of the mammary circulation, and especially understanding of the course and function of the lateral thoracic artery, will guard the surgeons against the consequences resulting from damage to the blood supply. He, therefore, recommends the following precautions:

1. The periareolar incision must be superficial and the excess areolar tissue must be resected as close as possible to

3. Excision of internal half of breast should be avoided to preserve the internal mammary artery.

4. Because of the lateral thoracic artery, the resection of the external half of the breast is also contraindicated.

5. Excision of gland is best done in the midline between the main vascular pedicles (upper quadrants) and in the external lower quadrant.

In large hypertrophies, Maliniac advocates reconstruction in two stages. First stage: subcutaneous transposition of the central part of the breast and nipple and

a wedge-shaped excision from upper pole of the gland which does not disturb the blood supply. Second stage: six to eight weeks later, removal of excess gland and skin, eliminating thus the danger of necrosis.

Maliniac gives account of preoperative preparation of the patient including local markings. Describes modifications of previously published surgical procedures and recommends reconstruction in one stage in cases with moderate ptosis.

He stresses that contour of the breast should be determined mainly by the shape of the adjusted gland and not by the skin alone.

## SKIN GRAFTING

### The General Surgeon

Urkov<sup>12</sup> urges the general surgeon to use split or even full thickness grafts when indicated, especially with a view of securing coverage in surface wounds. Burns, automobile accidents, industrial accidents, and surgical defects should be done just as quickly as wound conditions permit. Excellent results can be anticipated if strict application of technical principles are adhered to, hospitalization periods can be reduced, contractures prevented, and the need for later plastic surgery made unnecessary.

The author discusses in detail the thickness and the reason for the use of various free skin grafts; the condition in which the wound should be at the time of grafting; his technic of preparing the donor site; the various grafts and post-operative dressings, and care indicated under various circumstances.

### Biopsy as an Accurate Guide to Decision of Early Skin Grafting

Pritchard<sup>13</sup> advocated histological examinations of tissues prior to skin graft-

ing in burns to establish the status of the wound scientifically. With well-advanced healing, no grafting was needed.

When rapid frozen section biopsies indicated the need of it, grafting could be carried out without delay.

Some interesting slides were reproduced; use of biopsy for determining the needs of skin grafting was satisfactory.

(Reviewer—Occasionally, when in doubt, a magnifying glass helps determine if grafting is necessary.)

### Immediate Skin Graft Following Injuries

Many wounds, compound fractures as well as soft tissue injuries, abrasions, traumatic amputation of finger, etc., cannot be closed primarily because of loss of soft parts. Primary healing, then, must be achieved by means of skin grafting. Split skin grafts can be applied after surgical cleansing of the wound, and "pocket" grafts are used by the author for injured surfaces, such as dorsum of the hand. In compound fractures of legs or forearms, when primary closure of the wound is impossible, relaxation incisions are made lateral to the wound in order to bring sufficient covering material over the bone. The relaxation incision in turn may be covered with a split thickness graft.

In cases where extensive débridement is indicated, as in much contaminated wounds, the resulting defect can be covered by a graft at the time of débridement.

The author<sup>14</sup> describes his surgical technic and gives details of pre- and post-operative care. His photographs include one in which an open compound fracture of the leg was successfully treated by his described technic. A Stader—external fixation—apparatus is *in situ* (Fig. 12).

### A Routine for Early Skin Grafting of Deep Burns

This author<sup>15</sup> is primarily interested in the late management of burns, some such injuries involving nerves, bones, etc., in addition to soft parts. The author's technic of treating burns is described and it is pointed out that grafting should be done as early as possible, sometimes after four to six days. The author agrees, however, that later grafts or the "second grafting" are more suc-

are safer, more comfortable to the patient, and promote healing by preventing the accumulation of fluids in the tissues. The dressing used is described and also the treatment for concomitant local infection if present.

### Simplification of Split-Skin Grafting—Gum Acacia Technic

Rubin<sup>16</sup> advocates the use of *acacia* as an adhesive in the endeavor to simplify the laborious and time-consuming

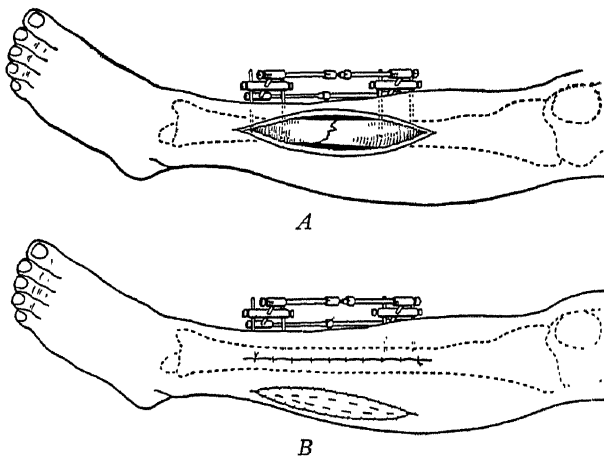


Fig. 12—*A*, above, Compound fracture of the tibia and fibula. The wound is meticulously cleansed and the fracture reduced under visualization. It is necessary to enlarge the wound to carry out this procedure. Most important single feature in treatment is thorough mechanical cleansing and débridement. *B*, below, Because of swelling, the operative wound could not be closed until a relaxing incision was made below. The open wound at the site of this secondary incision was then covered with a partial thickness skin graft from the thigh. (King, M. K.: Surg., Gynec. & Obst. 81: 75 (July) 1945.)

cessful since infection is more controlled. He uses split skin graft with *Padgett's dermatome* or the *Blair-Brown knife* with a roller attachment, the latter to be preferred when the area is extensive. He sutures only large dermatome sheets in order to stretch the graft, and believes grafts become firmly adherent within a few minutes after being placed because the necessary substances for adherence are present in the wound itself.

Rawles has not felt any demonstrable improvement when acacia gum solution was used. He always applies pressure dressings, and feels that dry dressings

suturing, often necessary; and to overcome marked postoperative discomfort experienced by the patient, as a result of pressure dressings currently employed following the use of skin grafts.

The *Padgett's dermatome* is used for cutting the grafts and a 50 per cent *gum acacia solution*, as recommended as a nerve graft "glue" by other authors, is used as an adhesive. The gum acacia solution is nonirritating.

Gum acacia solution: Powdered gum acacia, U.S.P., added to boiling water until a 50 per cent colloidal solution is formed. This mucilaginous solution is autoclaved for fifteen minutes under fifteen pounds pressure.

The technic of application is described. It is simple. Grafts thus treated "took" over fascia, fat, muscle, granulations, and scar tissue. Primary trimming of the recipient area is not essential. Bleeding must be controlled to secure taking of grafts. The skin surrounding the wound is painted with *tincture of merthiolate*; the wound itself is never washed with any solution.

Grafts about the face and hands are covered solely with one layer of *boric acid gauze* and a wire ladder splint or cage is fashioned over the graft to protect it against trauma.

The postoperative care is outlined. This technic is said to have been utilized in a large number of cases and very few failures have been met with in spite of apparently gross contamination of most wounds. *Acacia* evidently offers no barrier toward the normal process of healing. The cutting short of the operating time and the omission of cumbersome pressure dressings are some of the reasons advocated in favor of advancing this technic.

### Resplitting Split-Thickness Grafts with the Dermatome

Zintel<sup>17</sup> describes a method of "resplitting" a "split-skin graft." By using such grafts, the area to be grafted can measure two to three times the size of the donor area. The inner layer of the split grafts becomes completely epithelialized in about the same time as the donor area. Author believes that this technic is important to cover large skin defects as rapidly and as completely as possible so as to reduce morbidity and mortality.

In order to make two layers out of one layer of graft, the graft is split again while still adherent to the drum. The details of this procedure are given. The author covers the donor and recipient

areas with paraffin gauze. The dermatome must be used correctly during the initial step so that the original graft may remain well posed upon the drum during the process of resplitting.

### Full-Thickness Grafts

Full-thickness grafts from the neck and clavicular region<sup>18</sup> have been found to give superior results in the repair of facial defects. The amount of skin available is limited, but there is enough for the main areas for use of neck grafts, viz., the eyelids, the canthal area, about the ala nasi, over the nose, about the lips, and the angle of the mouth.

When boardlike scars of the eyelid are repaired with skin from the neck, the function and the color of the grafted area are improved; there is natural redness in the graft and pigment injection for color matching is not necessary. Relief from the scar fixation and the return of softness and pliability is often dramatic. The grafted area develops good kinesis and function remains excellent.

Grafts usually suffice for burns; flaps can be used and no permanent severe trouble results at the donor site.

The technic is described (Figs. 13 and 14) and photographs of patients before and after surgery are shown (Figs. 15A and 15B).

### The Use of Skin Flaps in the Repair of Scarred or Ulcerative Defects Over Bone and Tendons

A series of ninety-seven cases of chronic ulcerative lesions or deep adherent scars was corrected by means of skin flaps. A few lesions were on the head or body but most were upon the extremities. Padgett and Gaskins<sup>19</sup> advocate the use of skin flaps (skin and subcutaneous tissue) as necessary to insure viable coverings for chronic ulcers which are lying directly over bone or heavy

tendons, or if they are surrounded by deep unyielding scars. Skin plus subcutaneous tissues make the best coverage when resistance against trauma is of special importance and when secondary surgical intervention—repair of nerves, bone, etc.—is anticipated. The imme-

diate coverage of the resultant aseptic, denuded bed of the flap by a skin graft is emphasized.

They summarize briefly the various skin flap transfer methods. The *direct transfer* by which skin flaps are elevated from the bed and transferred into

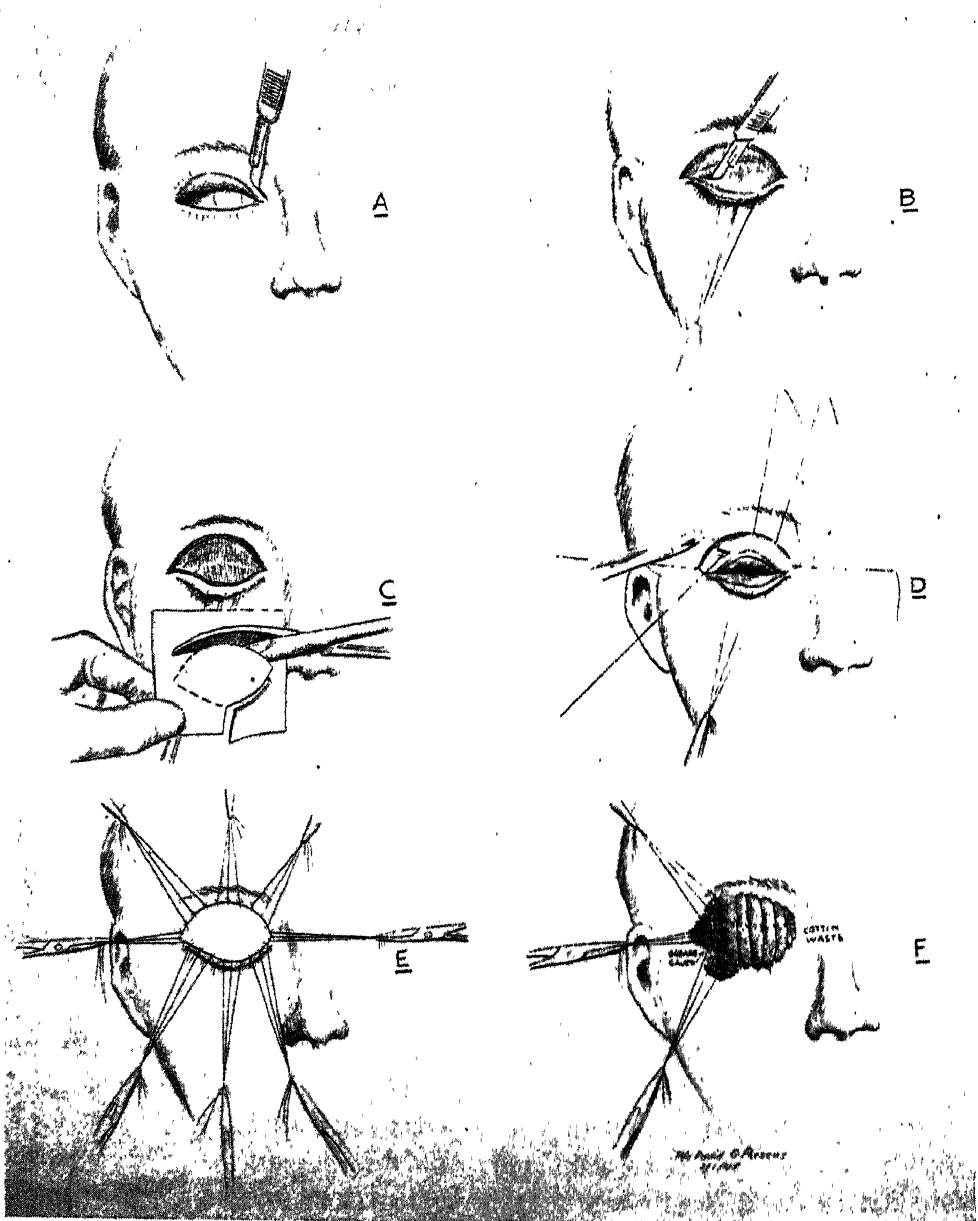


Fig. 13—Contracted area opened; surface and deep scar removed as necessary, to allow a little more than normal expanse. Where pressure alone cannot be relied on—as on the lids—the fixation is obtained and the proper opening of the area and the proper stretch of the graft obtained by the long sutures being tied over cotton mechanics' waste carefully packed into place, after covering the area with fine mesh grease gauze. (Brown, J. B. and Cannon, B.: Ann. of Surg. 121: 639 (May) 1945.)

their new situation at the first operation. (The various modifications of transfers are destined to increase circulation.) The *delayed transfers* without formation of a tube, and the *tubed pedicle skin flap*.

It is to be remembered that a simple skin graft requires usually but one operation, whereas repair by skin flap

thelial surfaces plus some thickness, such as in repair of the nose, the cheeks, the lips, etc.

Authors analyze cases with skull flaps (cover bare bone or dura), flaps for fingers; hands or arms and flaps of the lower extremity; about the thigh, the leg, or the foot; when due to trauma, osteo-

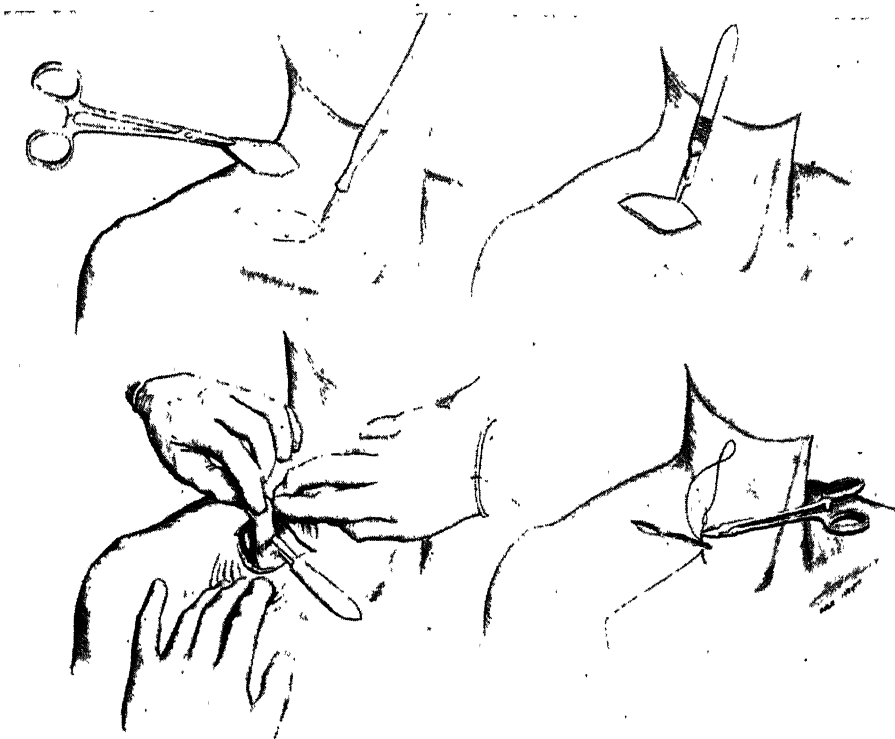


Fig. 14—Celluloid or pliofilm pattern marked on neck; tension produced by assistants for ease of removal; fingers hold graft to avoid crushing. Wound closed. (Brown, J. B. and Cannon, B.: Ann. of Surg. 121: 639 (May) 1945.)

calls for at least two, and often for more, operative procedures. Nerve innervation occurs more rapidly in skin grafts.

Large varicose ulcers give very good results after wide excision of the scar followed by skin grafting. Skin flaps are recommended as more advantageous to cover exposed tendons, nerves, and bones, to cover certain bases with deficient blood supply (irradiation ulcers and sloughs), to facilitate future repair of nerves or tendons, etc., and for building parts requiring two soft pliable epi-

myelitis, burns, and extensive irradiation for previous lesions.

In a good number of cases, skin flaps were taken from the calf of the leg and transferred to the opposite leg with good results. The authors believe that direct transfer saves much time and many operative procedures.

If there is objection to using the calf as donor site, the anterior, medial, or posterior thigh region can be used, and if a flap is to cover such areas as the heel, the external malleoli, or the tendo



achilles, skin flaps from the anterior thigh may be used and such flaps do not need long pedicles. To cover the external malleolus, the anterior foot, or the external tibial region, considerable length to the flap may be required; such flaps, therefore, should be delayed. The details of cutting and fixation of the flap are also described. A few comments are forwarded on correction for plantar de-

tions of larger defects of the ala and the tip of the nose. Author contends that flaps from the arm or the cervical region, as a rule, do not blend well with the rest of the nose; that forehead flaps, with inclusion of the supraorbital or the anterior branch of the superficial temporal artery, usually leave considerable scarring on the forehead, and also a noticeable patch where the free full thickness

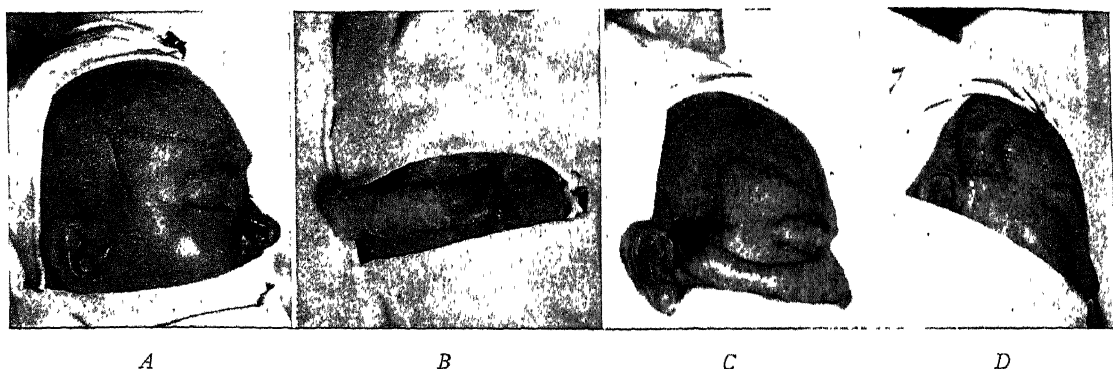


Fig. 16—*A*, The defect in the right side of the nose and cheek and inner canthus may be noted. There is a loss of the right half of the nose and of a portion of the bridge and of the cheek. A sickle flap has been elevated and the distal end has been lined with a skin graft to line the part of the flap that will reconstruct the ala and right side of the nose. *B*, The flap has been brought down to the nose. That part which is to reconstruct the nose is lined with a skin graft. The flap has been tubed by means of fine mesh gauze bandage. *C*, The defect in the forehead and scalp has been skin-grafted. The flap has been tubed by means of fine mesh gauze bandage. Before being replaced, flap is cut halfway across and then resutured at the point to be sutured to cheek in order to insure the blood supply on the new skin over the nose. *D*, The flap has been replaced and stretched so that it is not necessary to leave more than a small skin graft on the forehead below the hairline. The reconstructed portion of the nose has been sutured to the cheek. (New, G. B.: *Surg., Gynec. & Obst.* 80: 497 (May) 1945.)

fects caused by excisions or irradiation of plantar warts or corns, and in some instances a flap was rotated into the defect bed. To avoid trauma and ulcer formation of the newly transplanted regions patient should be advised to use crutches or a cane, the shoes must be well adjusted and padded until nerve supply has been returned.

#### Sickle Flap for Nasal Reconstruction

New<sup>20</sup> recommends a "sickle" flap in order to secure a good color match and claims that the defect resulting in the forehead is very little noticed; this procedure could be applied in reconstruc-

tion of larger defects of the ala and the tip of the nose.

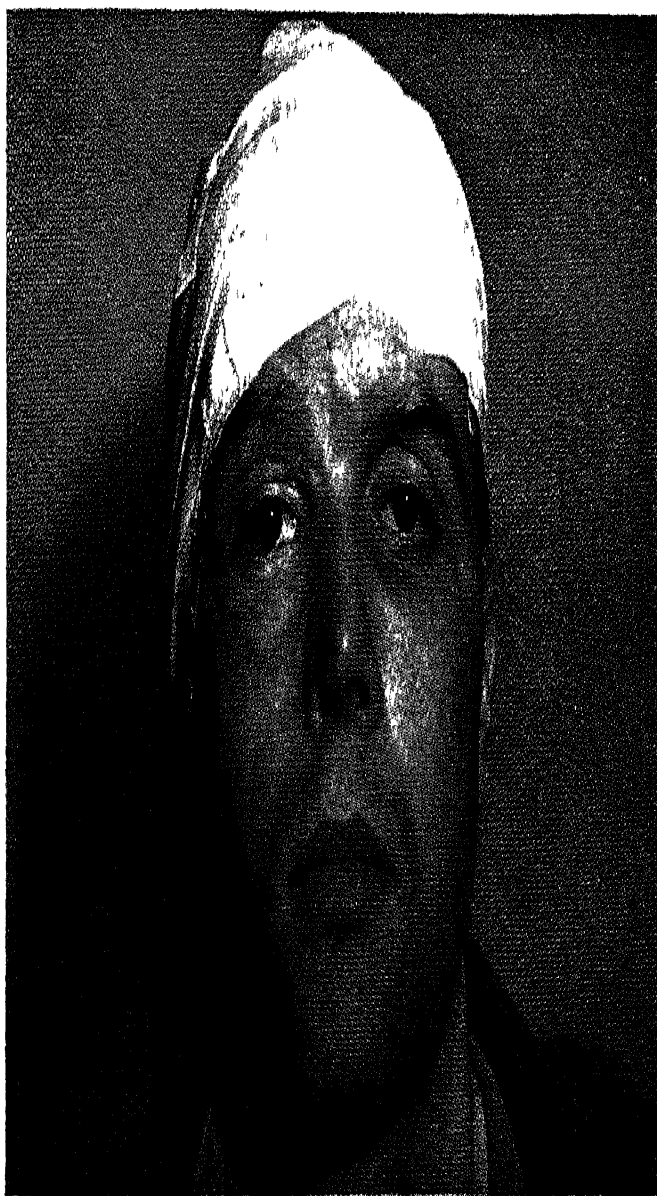
For total rhinoplasty, this author prefers an "up and down" forehead flap using the supraorbital vessels on one side as the pedicle, and he has used his sickle flap method in total rhinoplasties with success. The author describes the technic (Fig. 16).

#### New Design for Raising a Tubed Pedicled Flap

The author<sup>21</sup> feels that by using two straight parallel incisions as customarily described for raising a tubed pedicled graft there is reason for concern about



*A*



*B*

Fig. 15—*A* and *B*, Restoration of lid skin and function, and fairly normal color match with graft from neck. (Brown, J. B. and Cannon, B.: Ann. of Surg. 121 : 639 (May) 1945.)



the fact that the pedicle flap lies exactly over the donor area, *i. e.*, the suture line on the undersurface of the tube lies directly over the suture line of the donor area. He feels that it is not unusual that in suturing the corners, a certain degree of tension exists and that short tubes are difficult to suture and that complications are harder to deal with.

The new technic advocates cutting of the tube in a curve (Fig. 17, *A* and *B*)

more easily possible to care for both donor and tube suture lines. Additional length of the tube gained makes for easier closure of the corners and they themselves show better inclination to heal.

### Tattooing of Free-Skin Grafts and Pedicle Flaps

The color of skin is partially due to the presence of certain pigments, as in

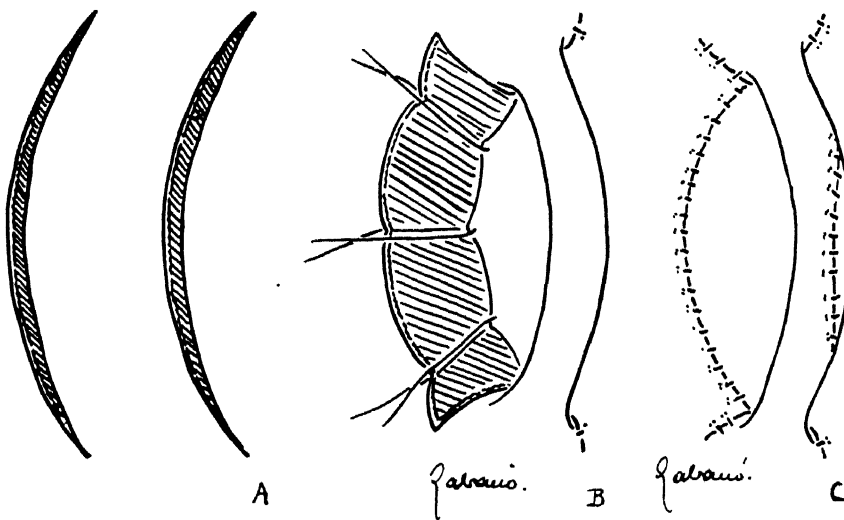


Fig. 17—A method devised by the author. *A*, Two parallel curves starting and finishing at the same level mark the edges of the pedicle. The skin is raised and rolled in. Radius of the inside curve is 5.5 cm. *B*, The stitches of the donor area are not inserted in the symmetrical points but radially, with the object of bringing the flap more to the side of the center of the curvature. *C*, All the sutures are in place. The central sutures of the flap are at the edge over the flap. The sutures of the corners and of the tubed pedicle flap are described in the text and additional illustrations. (Gabarro, P.: *Surgery* 18:732 (Dec.) 1945.)

instead of straight. The curvature of the flap should be adapted to the size of the flap and local condition of the blood supply. The radius of the curve can be shorter, the smaller the pedicle, since in these small flaps the blood supply is not likely to suffer.

Gabarro then gives detailed account of suturing the edges in respective position to tube (Fig. 17*B*) and adds that, once finished, the tubed pedicle stands quite easily away from the donor area. Fig. 17*C* illustrates the finished tube. This type of tube construction makes it

Negroes or dark-complexioned individuals.

The author<sup>22</sup> believes that whether skin transplanted to the face is whiter or darker, absence of the red tone is the chief factor in the color contrast. Since the use of cosmetics to enhance the appearance after plastic surgery is especially unsatisfactory with men, the author has for the past eight years injected permanent pigments into the derma. He considers the procedure and the result a safe and satisfactory cosmetic adjunct to surgery. He refers to

the tattooing of white corneal scars which causes considerable improvement to the appearance of the eye.

The pigments employed for tattooing must be nonpoisonous, nonirritating to tissues, and must be extremely insoluble and inert toward body metabolism; they are provided by the firms that supply tattooing equipment to professional practitioners.

**Technic of Tattooing**—The area and the instruments are prepared as for surgery; the pigments are autoclaved. The procedure is carried out under local anesthesia; it is less painful on a graft which has not yet regained its sensation. Hard scarred areas are less amenable to pigment injections and it is better to wait until skin grafts become flexible. Blending of the pigments to the ideal color requires a little experience.

Author reports improvement in all his cases undertaken and records no complications. Patients apparently regard this procedure as worth while.

### Direct Flap Repair of Defects of the Arm and Hand

The authors<sup>23</sup> advocate and discuss the use of direct short but broad pedicled flaps from the chest or the abdomen (Figs. 18A and 18B). They prefer the direct flap to the delayed or tube flap in injuries to hands and arms. They have carried out this procedure in a large number of cases where gunshot, shell fragments, and other types of wounds leave large surface defects and extensive, crippling scars. By this direct technic, much hospital time can be saved and the opportunities for secondary repair of bone, tendon, nerves, etc., is afforded much earlier. When foils, wires, screws, plates, or bone grafts must be used adequate protective coverage is provided, which renders this procedure especially important in the preliminary preparation

for many orthopedic and neurological repairs.

Authors discuss the crippling caused by "through-and-through" injuries; the need for adequate resection of deep and surface scars into an area that will furnish good circulation, and the planning of a serviceable surface closure which precludes a satisfactory blood supply (Figs. 18A and 18B).

They point out that when direct flaps are used within the first few days of injury, tendon and bone fragments can be saved, bony union advanced and scar tissue contracture, due to inadequate support, can be prevented.

They show importance of accurate recording of arm and hand injury, including separate notes for each finger. They place special emphasis on sensory findings, pin pricks, since decisions for saving or losing fingers may depend on such recordings, which, while tedious, yet are very useful in the operating room, especially when patients are anesthetized.

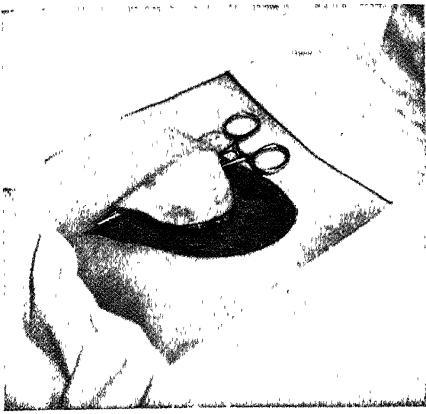
The authors describe very briefly technic of wound preparation; the choice of a suitable location for the flap; the preparation of the bed; the suturing of the flap; the pressure dressings; the use of splints and the treatment of the donor site and the occasional need for a double pedicled graft. They favor free skin grafts to bulky flaps on fingers and on the palms, and suggest that flaps be thinned out, if needed, at the time of deep structural repair.

Brown *et al.* point out that sensation develops surprisingly well in many flaps.

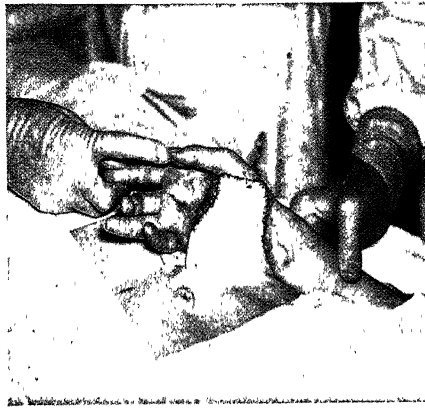
Authors suggest the use of letters for bones and joints of hands to simplify the terms.

### Skin Grafts in Traumatic Osteomyelitis

Kelly and Rosati<sup>24</sup> summarize in a very abbreviated way contributions pre-



A



B

Fig 18—Multiple-shell fragment wounds of hand with resultant fibrosis. Widespread dissection with removal of shell fragments encountered. Repair with direct flap detached in 18 days. (Brown, Col J B., *et al.*: Ann. Surg 122: 706 (Oct.) 1945.)



viously made toward the use of skin grafts in traumatic osteomyelitis. The authors explain the technic which they consider ideal. Some major points of the technic are as follows:

The wound is first saucerized; all unhealthy, scarred, or otherwise devitalized tissues and all foreign bodies are removed *en bloc* but may be removed, if necessary, in stages. Any bony under-

skin grafts are secured by the dermatome. The placing of the grafts and the types of postoperative dressings used are described. It usually requires eight weeks before the entire saucerized wound surface is completely covered by this skin graft. The possibility of replacing the primary skin graft by a more durable, more resistant, more permanent coverage must be borne in mind. The

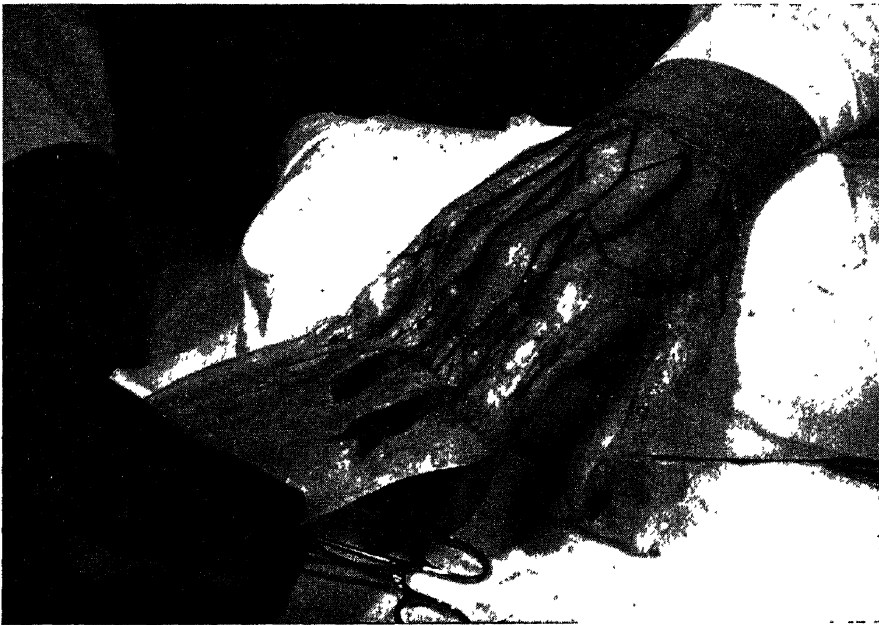


Fig. 19—"Peeling" off scar epithelium. (Farmer, Wing. Comdr. A. W. and Woolhouse, Surg. Lt. Comdr. F. M.: *Ann. Surg.* 122: 39 (July) 1945.)

cuts are carefully removed. If important structures (tendons, muscles, etc.) are exposed, local healthy skin flaps are shifted to cover them over. The saucerized wound is packed firmly and a cast is applied as recommended by Orr but no fat-containing substances are used (since they are known to interfere considerably with vascularization). Four days after saucerization, usually when granulation tissues have formed on the relatively avascular cortical bone, skin grafting is performed. Simultaneous sequestrectomy and skin grafting can occasionally be carried out safely. The

results of the technic advised have been almost uniformly beneficial.

### Skin Graft of Dorsum of Hand

Extensive war burns of the hand may call for total replacement of the dorsum by an intermediate skin graft. The junction of several small pieces of graft may not be esthetic and if keloids form the function is impaired. The use of a large one-piece skin graft accurately cut and fitted is most desirable.

**Technic**—Author removed scar from dorsum of hand and the fingers and placed the scar tissue upon the graft still



adherent to the *Padgett dermatome*—*raw area toward epidermis*—to be sure. He then cuts the skin graft on the drum with a scalpel by following the contour of the scar tissue pattern. The correctly fashioned graft is then transferred to the hand and secured to the wound by a continuous running suture. A pressure dressing is applied.<sup>25</sup>

power of joints where tendon and joint capsule destruction would otherwise precipitate extensive joint stiffness or even ankylosis.

Thick split skin grafts were mostly used and about the only need for pedicled grafts were cases where a layer of fat was needed to protect important structures and when secondary repairs



Fig. 20—Cutting for graft in interdigital spaces to avoid subsequent webbing. (Farmer, Wing. Comdr. A. W. and Woolhouse, Surg. Lt. Comdr. F. M.: *Ann. Surg.* 122: 39 (July) 1945.)

### Resurfacing of Dorsum of Hand Following Burns

Farmer and Woolhouse<sup>26</sup> describe their technic of "resurfacing" the dorsum of the hand following injury to the original skin by burns. A variety of lesions, including exposed tendons and open joints, were thus treated. The majority of the recipient areas were contaminated granulating surfaces, yet the "take" was good. The authors' resurfacing procedure aims at restoration of the hand toward original functional ability, good wearing surfaces, and good cosmetic results.

Prompt resurfacing followed by tendon grafting is advocated to restore the

with free tendon grafts had to be carried out.

The authors discuss in detail the preoperative findings of lesions, the pre- and postoperative therapy and their technic of débridement. They illustrate how in clean cases the scar epithelium can be "peeled" off (Fig. 19), and how the graft is fitted onto the wound and sutured *in situ* (Fig. 20). The authors do not usually puncture the grafts. They use a light, even pressure dressing which they describe; also a light plaster cast which helps to keep the wrist and metacarpophalangeal joints in approximately full flexion.

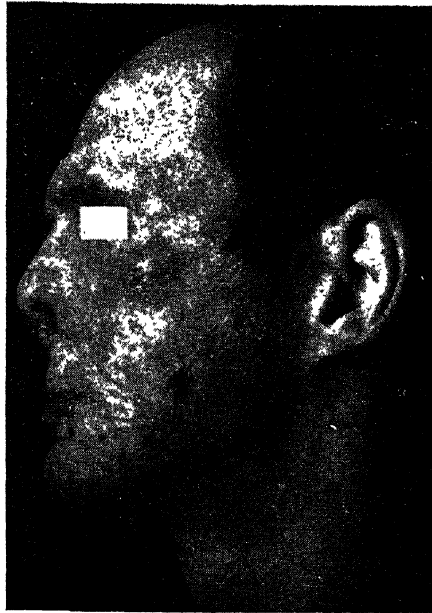


Fig. 21—Showing condition of nose following removal of squamous-cell carcinoma of nasal tip. (Jenkins, H. P.: *Ann. Surg.* 122:1042 (Dec) 1945.)



Fig. 22—Showing result of extensive skin grafts to face nine months after completion. The nose was reconstructed from a pedicle from the arm. The skin of the face was replaced from ear to ear and from below the eyes to beneath the mandible by dermatome skin grafts. (Jenkins, H. P.: *Ann. Surg.* 122:1042 (Dec.) 1945.)

The authors recommend immobilization of fingers in *early stages of burns*; they warn against the grave disabilities resulting from prolonged immobilization, and believe that full usefulness can be restored to all promptly resurfaced hands

multiple areas of squamous cell carcinomata. Split skin grafts were used to replace the lesions of the entire face. (From ear to ear and from just below the eye to beneath the chin and along the underside of the mandible.)

Fig. 23.



Fig. 24.



Fig. 23—The "bridge" flap has been mobilized, its edges supported by hooks. Note its thickness, due to fat pad under skin. It is now held over tibia. Note fat remaining on calf muscles. The resulting fresh defect is obvious. Note its somewhat larger extent than the original ulcer. The still-attached ulcer tissue is seen held by Ellis clamps for contrast. (Pick, J. F.: Am. J. Surg. 69: 25 (July) 1945.)

Fig. 24—The ulcer tissue has been completely detached. The inner side of flap has been approximated to what was the medial aspect of the ulcer. The size of the newly created raw surface can be compared with the six-inch hemostat. (Pick, J. F.: Am. J. Surg. 69: 25 (July) 1945.)

unless irreparable joint damage is already present.

### Subtotal Replacement of the Skin of the Face

Author<sup>27</sup> presents a case of actinodermatitis from roentgen ray with mul-

A nasal reconstruction was performed in multiple stages for which a pedicled graft was used. Some preliminary surgery, including a neck resection, was carried out. Under local anesthesia all the damaged skin covering the face and lips was excised and the

resulting wound defects were covered with dermatome grafts.

Author describes the dissection of the cheeks and lips and the suturation of the grafts which he did *not* fenestrate. The primary pressure dressing was changed after two weeks; the graft, at this time, was found to be in relatively good condition. The other half of the face was done later; the replacement of the upper lip concluded the procedure. The pressure dressing on the upper lip did not prove especially satisfactory, but the lip finally healed without requiring further grafting. The scarring of the upper lip where it was joined with the grafts of the cheeks was not satisfactory at first but improved with time. The cosmetic result was satisfactory (Figs. 21 and 22).

The author believes that such extensive removal and replacement of skin of the face is justified in cases of severe roentgen ray burns and should be carried out before carcinomatous changes are definitely in evidence.

### Dermoplasty of War Wounds of the Lower Leg

In war, as in peacetime, it is imperative that unstable extensive scars, indolent ulcers, gaping compound wounds with perhaps visible bone should be cared for by surgical revision. Pick<sup>28</sup> states that application of some type of free skin grafts, *too* commonly only a split graft, makes an open into a closed wound which is good only in principle because such covering is anatomically inferior and therefore physiologically inadequate and affords no promise of ultimate functional excellency. The use of skin *flaps* for covering important structures is stressed.

When compound fractures, treated by the open method, terminate in nonunion,

ulceration, and unstable healing with deformity, the excision of dead bone plus the damaged area involves so much tissue that only bare bone or tendon remains as a bed for grafting. Such extensive and deep defects cannot be satisfactorily covered even by full thickness skin. A flap is therefore raised (Fig. 23). Much care is exercised to leave the superficial fascia attached to the double pedicled flap (Fig. 24). This bridge of tissues with its own arterial and venous circulation conserved is moved to cover over the defect (Fig. 23). The resulting defect is closed directly if possible; any residual defect is covered with a graft, most preferably of the full thickness type, giving not only better cosmetic but eventually better functional results. The author does not believe that the use of single pedicle flaps, especially from the contralateral extremity, is a good practice. The author describes his method of pressure dressings and of the pre- and postoperative care.<sup>28</sup>

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## THORACIC SURGERY

CHARLES P. BAILEY, M.D., M.Sc.

### Acute Pulmonary Edema

**Treatment**—Ansbro<sup>1</sup> recommends the use of positive pressure respiration in pulmonary edema for the following reasons:

1. The effect of inhaling a gas under increased pressure is to decrease the pathologically elevated negative intrapulmonary pressure in cases of obstructive dyspnea. This heightened negative pressure tends to promote oozing of serum from pulmonary capillaries.

2. The lumen of the smaller bronchioles is less constricted during inhalation of an atmosphere under positive pressure.

3. The increased intrapulmonary pressure diminishes the accumulation of blood in the lungs by exercising to a variable extent a retarding effect on the entrance of blood into the right heart (like a phlebotomy).

4. The inhalation of a gas under positive pressure exerts a direct opposing pressure on the pulmonary capillaries which tend to retard the outlet of serum from them. It opposes in a direct way the increased hydrostatic pressure in the pulmonary capillaries as much as bleeding anywhere is stopped by mechanical pressure.

Two cases are cited: A twenty-five-year-old physician with depression from medication developed pulmonary edema

not relieved by oxygen mask, tent, or catheter. Bronchoscopy was found useless. Five minutes of positive pressure oxygen was applied. In five minutes, the cyanosis was gone. This was repeatable. He finally recovered after six days of therapy.

The other case was a tracheotomy after thyroidectomy. Foamy mucus from the tube threatened asphyxia. Positive pressure oxygen was applied directly through the tracheotomy tube with dramatic effects.

### Penicillin in Infections of the Lungs and Bronchi

Kay and Meade<sup>2</sup> report upon their experiences with penicillin in the treatment of ninety-three patients. Forty-five had bronchiectasis, seventeen had lung abscess, six had suppurative pneumonitis, nineteen had chronic bronchitis, and five had fungus infections of the lungs. At first, only intramuscular penicillin therapy was available but later intratracheal penicillin therapy was developed. In general, it is felt that the greater the degree of permanent tissue destruction and chronic infection, the less is the benefit from penicillin. Thus the best results were obtained in chronic bronchitis and minimal bronchiectasis. However, penicillin was of value in many of the chronic cases and in treatment of

acute exacerbation bronchopneumonia, etc. It is of value in preparing cases for operation and in decreasing postoperative complications.

The bacteria found by bronchoscopy in chronic infections of lungs and bronchi are varied. Usually there were mixtures of organisms, the most commonly found being alpha, beta, and gamma hemolytic streptococci, *Staphylococcus aureus*, and *Pseudomonas aeruginosa*. Anaerobic streptococci, fusiform bacilli, and spirochetes were more commonly found in patients with chronic lung abscesses and pulmonary suppuration.

The authors feel certain that penicillin is of no permanent value in the treatment of advanced bronchiectasis, but it frequently produces considerable temporary improvement. Recurrence of septic symptoms three to four weeks after cessation of penicillin therapy was the rule. Preoperatively, they feel it to be of great value.

Of the seventeen cases with chronic lung abscess, four required immediate surgical drainage. In one case, the abscess promptly healed under therapy. The others showed, as a whole, favorable response to penicillin therapy with reduction in sepsis, sputum, and the areas of pneumonitis shown on x-ray. However, as soon as therapy was discontinued, symptoms recurred.

Two of the cases, with fungus infections, had coccidiomycosis, one a *Monilia albicans* infection, and two actinomycosis. The first three showed no response to intramuscular penicillin. The actinomycotic patients had other organisms in their bronchi as well as actinomyces. They were partially improved by a combination of *penicillin* and *sulfonamides* but relapsed as soon as treatment was discontinued. Pulmonary resection was successfully employed in these two cases.

The cases of bronchitis, ulcerative hyperplasia, asthma, and catarrh showed some favorable response to intramuscular penicillin, but were dramatically improved following the intratracheal administration. These were all cases with long histories of bronchopneumonia, productive cough, and multiple hospitalizations over periods of years.

The intratracheal application of penicillin was employed by means of indirect laryngoscopy and a flexible laryngeal cannula. Three to 5 cc. of saline containing up to 10,000 Oxford units of sodium penicillin to the cubic centimeter was applied at the end of expiration once daily. The improvement following this therapy was apparently more marked than that obtained by the intramuscular route. The greatest improvement was seen in cases of bronchitis and minimal bronchiectasis.

Interestingly enough, pathological examinations in seventy-five lobectomy specimens failed to show any appreciable difference in the degree of infection in twenty-five cases without penicillin treatment as compared to fifty cases in which penicillin had been used.

There was an operative mortality in 100 lobectomies of 1 per cent.

The nonsurgical treatments at present include: *Rest, nutrition, and high vitamin diet, climate* (warm), *postural drainage* (very important), *systemic drugs* (colloidal iodine and silver, neoarsphenamine, creosote, sulfonamides, penicillin), *endobronchial application of drugs* (lipiodol, sulfonamides, penicillin), *bronchial irrigations, and vaccine therapy*.

*Operative treatment* consists of the removal of the diseased lung, lobe, or pulmonary segments. This is now a highly refined process requiring exact anatomical knowledge and usually embracing individual ligation of the hilar structures.

Highly skilled anesthesia is of great value in permitting a smooth operation and uneventful postoperative course. Postoperatively, the greatest attention should be devoted to encouraging the evacuation of bronchial secretions by cough, postural drainage, endotracheal catheter suction or formal bronchoscopy.

### Bronchopleural Fistula

Adams<sup>3</sup> advises the following technic to close a chronic bronchial fistula:

The latissimus dorsi is divided in the line of skin incision. Four ribs are resected over the fistula. Two intercostal nerves are cut, and an intercostal incision is made. A flap is thus made from the periosteal and intercostal tissue, pedicled below.

The next step is to cut around the fistulae or fistula, taking out a shallow V or saucer of visceral pleura and the ends of the draining bronchi. Communicate with adjacent bronchus if necessary. Then a running suture of chromicized catgut is used to close bronchial ends. This is run back again to make a cross-hatch suture.

The visceral pleura is then split and the lower layer of it sewed over the bronchus with interrupted Lembert sutures. The upper layer is next sewed over in imbricating fashion with interrupted mattress sutures.

The periosteal muscular flap is split and the parietal pleura discarded. The flap is then sewed to the visceral pleura, high up. This is covered with muscles (latissimus). Rubber drainage and sulfonamides (locally) are used.

### Bronchiectasis

Bradshaw and O'Neill<sup>4</sup> stress that this disease is by definition one associated with dilatation of the bronchi or of a bronchus. It may produce a uniform dilatation (cylindrical bronchiectasis), or areas of greater and lesser dilatations (sacular bronchiectasis). In addition to these bronchial dilatations, an infective element must also be present if the case is of clinical importance. There are also frequent peribronchial changes, such as fibrosis or areas of suppuration.

The ultimate etiology is disputable. Some cases seem definitely to be of congenital origin, perhaps allied to cystic disease. The occasional association of bronchiectasis with cystic disease of the pancreas or with clinical celiac disease may be considered evidence of congenital abnormality, or perhaps may suggest that a vitamin deficiency is concerned. Bronchial obstruction due to foreign bodies, tumors, stenosis, enlarged mediastinal lymph nodes, mediastinal tumors, cysts, or aneurysm can frequently be shown to have a direct cause and effect relationship in certain specific cases. Destructive inflammatory lesions of the lung, such as abscess, suppurative pneumonitis, fungus disease, and tuberculosis, commonly leave permanent bronchial dilatations. Thick, viscid secretions "drowning" a lobe after a pneumonic process, especially in children, may cause similar bronchial destruction. Blades and Dugan have shown that sometimes the bronchial dilatations following such inflammatory processes are transient, disappearing completely in four to six weeks. They have called this "pseudo-bronchiectasis." Chronic sinus disease is frequently seen in bronchiectatics. The bacteriology is variable, including usually the flora found in the oral cavity.

The clinical features are extremely variable. Some patients have a constant foul profuse sputum with much hard coughing, fever, cyanosis, hemoptysis, and frequent incapacitating bouts of severe pneumonitis. Others have almost no symptoms. The vast majority present symptoms of intermediate severity. Many patients only have sputum in the winter-time when respiratory infections are common.

Diagnosis is made upon the clinical history and the properly made bronchogram. Regardless of the technic employed, every bronchus in the pulmonary

system, at least down to the quaternary ones, must be properly outlined before an accurate anatomical diagnosis can be reached. If surgery is contemplated, this anatomical mapping is most important since a complete cure cannot be expected unless the entire area of disease is extirpated.

**Prognosis**—This is a much more serious disease than ordinarily believed. An early fatal termination is to be expected in most cases. Thus Perry and King in 1940 studied 211 patients with bronchiectasis, 31 per cent of whom died at the time of reporting, and 78 per cent of the deaths were directly due to bronchiectasis. Of the remaining 144 cases, 38 per cent were in excellent condition, 42 per cent in fair condition, 15 per cent in poor condition, and 5 per cent in very poor condition. Forty-one per cent of the dead died within five years of the disease.

### Fungus Infection

Pulmonary infection by various fungi has been known for some time, and various forms of medical treatments, including *x-ray therapy*, are employed. *Potassium iodide*, *thymol*, and the *sulfonamides* are frequently used. *Surgical removal* or *drainage* of fungus infection of other parts of the body is frequently employed. However, it is extremely rare for the pulmonary lesions to receive surgical therapy unless one includes *pneumothorax therapy* given under the mistaken diagnosis of pulmonary tuberculosis.

Dormer, Friedlander, Wiles, and Simson<sup>5</sup> report upon a case of *Cryptococcus histolytica* infection causing a large solitary tumor of the right lung. This was treated by surgical removal of the involved upper and middle lobes in a twelve-year-old child. The tourniquet technic was employed. The patient re-

sponded well at operation but twenty-three days later showed signs of meningitis (due to *Cryptococcus*). This failed to respond to sulfadiazine but rapidly cleared up under potassium iodide therapy. He was apparently well nine months after operation.

The editor had a very similar, as yet unreported, case in a nineteen-year-old boy which was treated by total pneumonectomy by the dissection technic. He recovered uneventfully and remains well twenty-six months after surgery.

These two surgical successes, in a condition usually considered fatal, suggest the advisability of applying *resection* therapy more widely in pulmonary mycosis.

Kay and Meade<sup>2</sup> have reported two cases of pulmonary actinomycosis successfully treated by resection.

Recently, because of increasing interest in pulmonary malignancy, the diagnostic and differential diagnostic features of this disease have been stressed. The result has been progressively earlier diagnosis and better therapeutic results.

### X-ray Studies

The various mass x-ray examinations of the chest which are now being carried out on an increasing scale in order to find unsuspected cases of early tuberculosis, and routine chest fluoroscopy of all patients in the outpatient clinics, as in the University of Chicago and other progressive institutions, are revealing many nontuberculous involvements of the chest. The lesions as seen on the roentgenogram are frequently small and nearly always nondiagnostic. Since they may represent pulmonary malignancy in an early and curable stage, the responsibility placed upon the clinician is greatly enhanced.

Bloch *et al.*<sup>6</sup> feel that such mass studies would be justified if only for the sole purpose of uncovering cardiovascu-



TABLE I

FINDINGS OF INTRATHORACIC TUMORS IN 15,000 PATIENTS. ROUTINE CHEST FLUOROSCOPY IN THE OUTPATIENT DEPARTMENT, UNIVERSITY OF CHICAGO CLINICS

Type of Tumor	Number	Per Cent of Patients Examined	Per Cent of Tumors Found
Metastatic Carcinoma	34	0.23	37.3
Primary Carcinoma ..	25	0.17	27.4
Lymphoma .....	19	0.13	21.0
Sarcoma.....	5	0.03	14.3
Undiagnosed.....	5	0.03	
Miscellaneous.....	3	0.02	
Dermoid Cyst			
Neurofibroma			
Hemangioma			
Totals.....	91	0.61	100

(Bloch, R. G., *et al.*: J. Thoracic Surg. 14: 83 (Apr.) 1945.)

lar disease and tumors. Of 15,000 patients so studied, 91, or six-tenths of 1 per cent were found to have intrathoracic neoplasms. Of these, 25 were proven to be primary bronchiogenic carcinomas.

It must be emphasized that these patients are nearly always without symptoms or physical signs directed toward the pathology. Bronchoscopic examination usually is noncommittal in these cases, especially in the peripheral tumors. Aspiration biopsy is difficult or impossible in these early lesions. Contrary to popular opinion, these lesions may not produce symptoms for months or even years<sup>2, 3</sup> after first detected. This is suggestive of the extreme chronicity of the tumor. The usual rapid downhill course in diagnosed cases is largely due to the late stage at which the diagnosis is ordinarily made.

The authors emphasize that even the finding of an early cavity does not rule out carcinoma. They feel that cavitation appears in as many as one third of all

cases of lung malignancy, and may appear very early (Figs. 1 and 2). This again emphasizes the inadequacy of the x-ray as a differential diagnostic method but in no way disputes its position as the primary case finding method.

They, therefore, feel that all cases of undiagnosed localized lung shadows should be surgically explored after a short period of observation if the patient's condition permits.

### Pulmonary Tuberculosis

**Bronchography** — During the past twenty years, the senior author of this series of articles has carried out over 2000 bronchographic studies in all stages of pulmonary tuberculosis at the King George V Hospital for tuberculosis, Durban, South Africa. His findings have been frequently at extreme variance to the accepted conceptions of the cause and pathology of tuberculosis at various stages.

Their conclusions run about like this:

1. Bronchography with iodized oil is safe in all stages of tuberculosis unless the patient has an idiosyncrasy to iodine or cocaine.

2. A living picture of the actual pathology present in pulmonary tuberculosis cannot be determined with any degree of accuracy from history, physical examination, conventional x-ray, bronchoscopy, and laboratory studies alone. Unless these are supplemented by bronchography in every case, the diagnosis, prognosis, and plan of therapy are based upon an inadequate understanding. The wide discrepancy is readily seen when bronchograms frequently reveal the presence of extensive bronchiectasis in apparently early cases. In certain cases, bronchography gives definite information contraindicating the use of collapse or perhaps any surgical therapy.

3. Block of some portion of the bronchial tree is invariably present in every case of pulmonary tuberculosis unless the area beyond the block has already broken down into a cavity. Even when there is the earliest demonstrable x-ray lesion, this block occurs, usually in the bronchioles. This earliest roentgen finding

is, therefore, due to a patchy atelectasis rather than an inflammatory infiltration as previously believed.

This bronchiolar block may be due to swelling of the bronchial mucosa (perhaps due to allergy) or to swelling of lymph nodes, causing bulge block of the bronchioles.

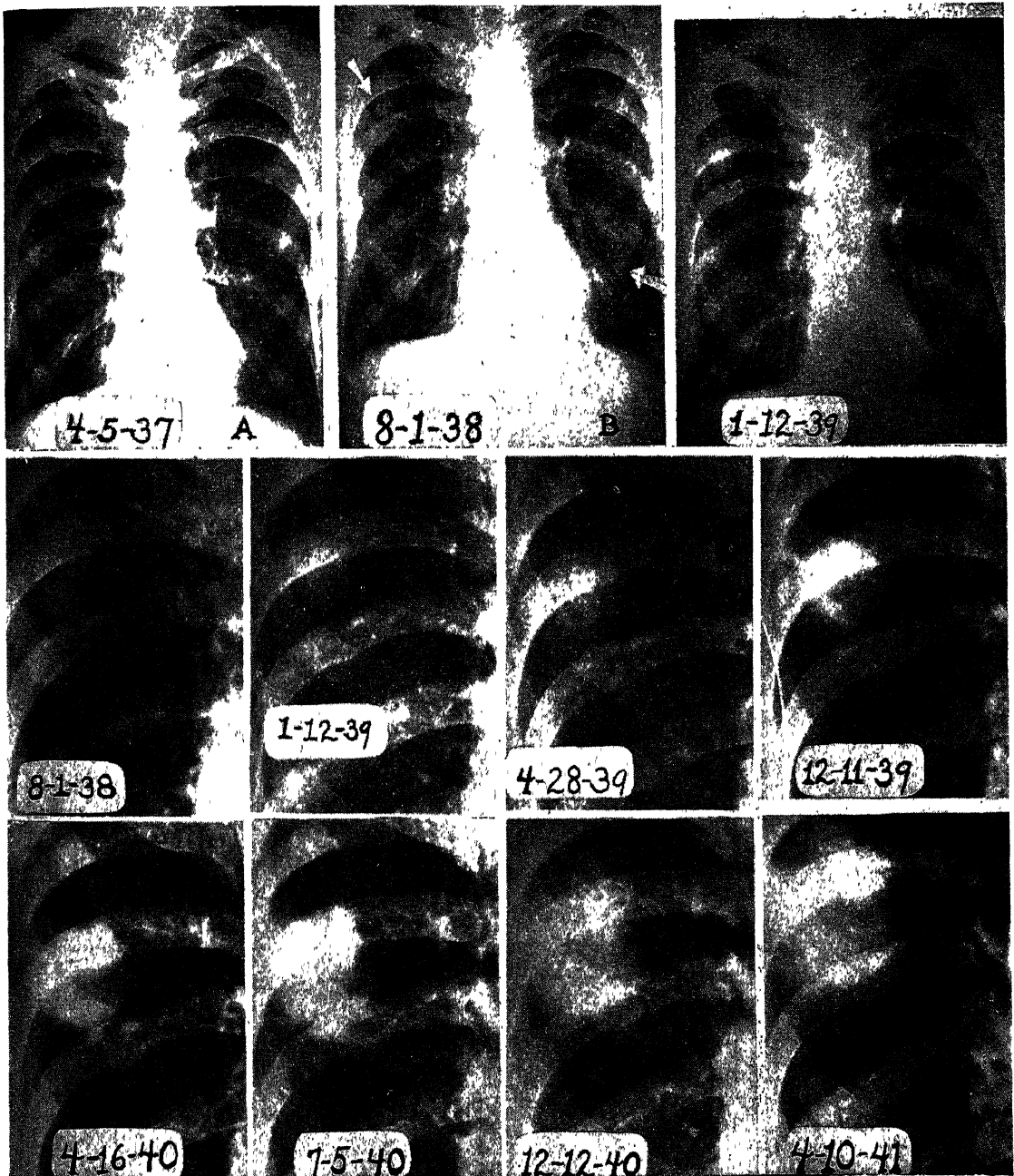


Fig. 1—(Bloch, R. G., *et al* : J. Thoracic Surg. 14: 83 (Apr.) 1945.)

4. As a result of the bronchial or bronchiolar block, there occurs cavitation or bronchiectasis and ultimately a distortion of the bronchial tree, due to fibrosis in the affected area. These changes, therefore, arise in exactly the

which it is clinically effective. One might think that since blockage of bronchioles and atelectasis are important factors in the production of bronchiectasis (Tannenbergh and Pinner, 1942), pneumothorax or other collapse measures which

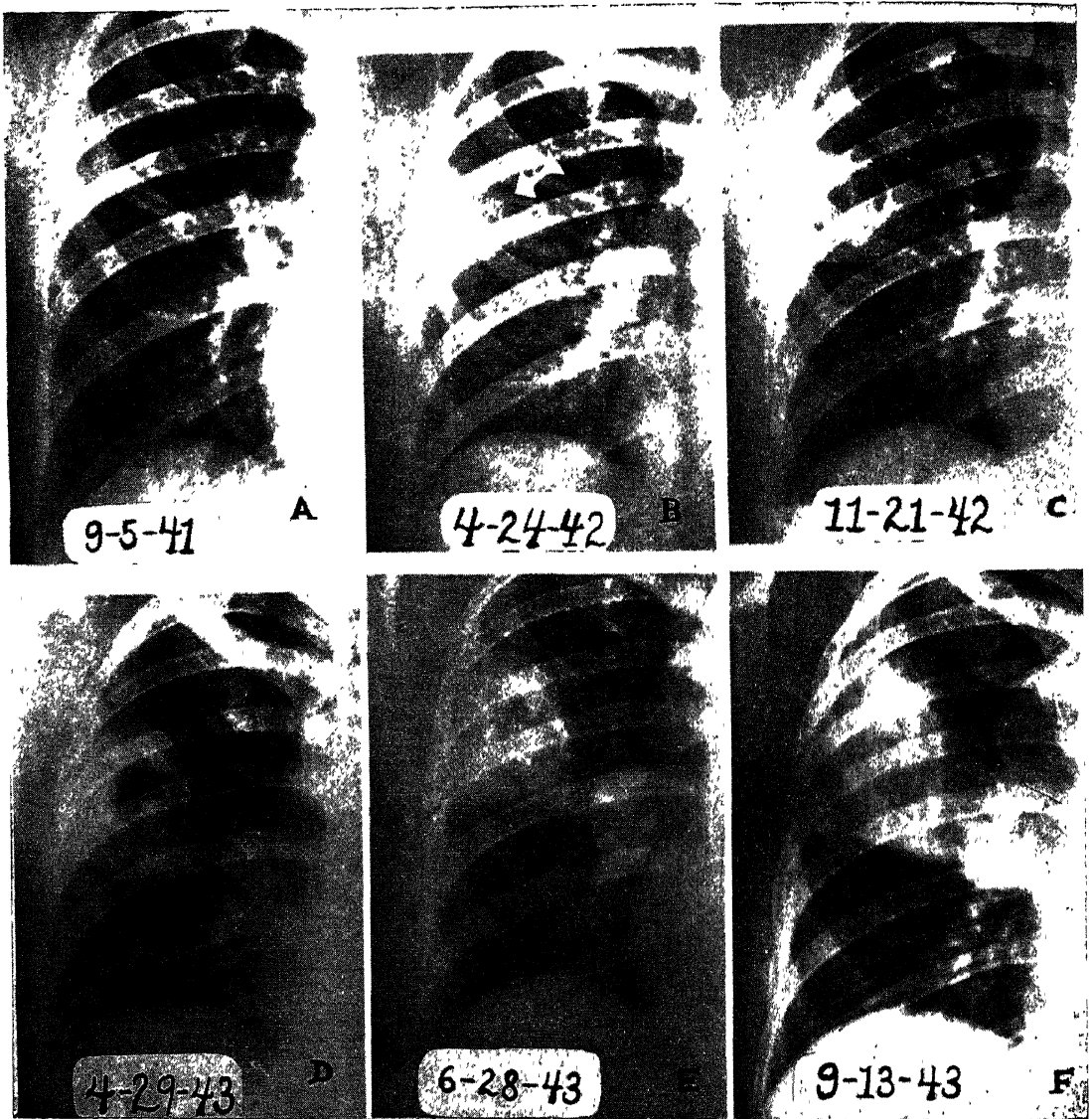


Fig 2—(Bloch, R. G., *et al.*: J. Thoracic Surg. 14: 83 (Apr.) 1945.)

same way as they do in nontuberculous bronchiectasis and pulmonary abscess.

5. Collapse therapy has been utilized extensively in the treatment of pulmonary tuberculosis. Yet no one has satisfactorily explained the mechanism by

tend toward the production of atelectasis would aggravate the production of bronchiectasis. Dormer, Friedlander, and Wiles<sup>7</sup> point out that in one case the tendency to collapse is central, in the other it is from the periphery. They

feel that the general retraction and shrinking of alveoli and connective tissue prevent further infection and tend to squeeze liquefied tuberculous material out of the blocked bronchioles, leaving them patent. They support this hypothesis by serial bronchographic studies on cases of early exudative disease. The alveolar pattern is found missing in the areas of infiltration and the bronchioles in those areas are blocked. Immediately after the institution of an uncomplicated pneumothorax, the blockage persists and the alveolar pattern of even the uninvolvement portions is not as marked as in a normal uncollapsed lung. But as refills are continued, fewer bronchioles are seen to be blocked and eventually they all become patent. The alveoli then fill in the diseased lobe except in the actual area of infiltration, where they remain permanently collapsed. These authors feel that healing takes place by fibrosis of the approximated thin walls of recent cavities and recent bronchiectatic cavities.

The authors have discussed the experimental work of Tannenberg and Pinner, which proved that the institution of artificial pneumothorax in a case of bronchial obstruction plus distal infection was of no value in preventing the development of bronchiectasis. They maintain that the obstruction of a bronchus by a foreign body or bronchial ligature is quite different from bronchial obstruction by viscid sputum (containing tubercle bacilli or other organisms). They believe that early institution of artificial pneumothorax permits expulsion of bronchial sputum plugs and therefore relieves the obstruction (whether in tuberculosis or postoperative atelectasis). Thus further development of bronchiectasis is prevented.

6. This reasoning is continued to explain the uselessness of pneumothorax or other collapse therapy in cases where

bronchial block persists in spite of this therapy (as in bronchial stenosis). Here the institution of pneumothorax leads to lobar or segmental atelectasis within the pneumothorax. Since the collapse therapy really accentuates the bronchial block in such cases, the patient's condition becomes worse.

7. Pneumothorax therapy should not be undertaken in cases in which bronchography shows long-standing thick-walled cavities or bronchiectasis. The same pathology persists after the treatment is concluded.

8. Pneumothorax with positive (above atmospheric) pressures is a relic of the past, and not only useless but dangerous.

9. Pneumothorax is not effective because of any resting of the collapsed lung. The movements of the treated lung in unilateral pneumothorax are greater than in the uncollapsed one. Part of this is due to swing of the mobile mediastinum. This is lessened in bilateral pneumothorax.

10. Even in rapidly developing lethal miliary tuberculosis, bronchiolar block is prominent, and both bronchiectasis and cavitation may rapidly develop. One of the reasons for rapid death is asphyxia because the air cannot get to the alveoli.

11. The recent cavity in the upper portion of the lung which will not respond to artificial pneumothorax is the ideal indication for thoracoplasty. *In all other stages of tuberculosis* the results from thoracoplasty cannot be predicted. Some cases emerge with a positive sputum and some with a negative, but one cannot predict this in advance. This opinion is indeed at variance with that of most phthisiologists who have thought that best thoracoplasty results were obtained in cases of some chronicity.

The authors believe that the problem is much more than the proposition of closing cavities. There is always bron-

chiectasis with the cavitation. Unsuspected bronchial block may exist in any case, and bring the most expertly performed thoracoplasty to failure.

12. After thoracoplasty, bronchiectasis remains in every case. Indeed, it is not infrequently greater than preoperatively. This bronchiectasis may or may not give rise to a positive sputum. Therefore, the authors feel that thoracoplasty in all but those cases of early cavity without bronchiectasis is a completely hit-or-miss affair. The end result is not due to the skill of the operator or the prognostic ability of the physician.

13. Discouraged by these variable results, the authors have tried the therapeutic effects of sulfonamides suspended in lipiodol instilled directly into the dilated bronchi. Remarkably, a considerable number of cases of sputum conversion have been obtained by this means. This has been observed in chronic cavity cases sometimes before and sometimes after collapse therapy. Two gm. of *sulfanilamide* or *sulfadiazine* may be suspended in 5 cc. of lipiodol. A much higher local concentration of the drug is obtained than possible by systemic therapy. It is possible by using this suspension to simultaneously perform both diagnostic studies and local therapy in the hope of sterilizing chronic tuberculous bronchiectatic areas and cavities. The authors also feel that sputum is routinely diminished in amount and infectivity by such treatment. Therefore, they recommend it routinely three days prior to the performance of a thoracoplasty. If such a preoperative treatment can lessen the danger of tuberculous spreads and extension of bronchiectasis during surgery, it is indeed a most valuable contribution to thoracic surgery.

**Surgical Treatment of Tension Cavities**—Certain cavities fail to col-

lapse in spite of surgical measures (pneumothorax, thoracoplasty) due to a valvular mechanism in the draining bronchus or at the junction of the bronchus and the cavity wall. This valve effect is usually due to an area of edema, granulations, or stenosis, with or without the addition of tenacious secretions within the bronchial lumen, often with associated bronchial spasm. Since the bronchus dilates on inspiration and contracts on expiration, air is readily trapped within the cavity. If there is a considerable increase in intrabronchial pressure as in coughing, air may be forced into a cavity under high pressure and trapped there. Since this pressure will be considerably greater than atmospheric, it would not be logical to expect cavitary closure with thoracoplasty or pneumothorax, even of the tension type.

These high intracavitary pressures may be directly measured by needling through the chest wall. Thus the nature of a suspected cavity may be determined in advance.

Since these cavities are due to a partial obstruction of the draining bronchus, they may alter in size at any time if the degree of obstruction becomes greater or less, thereby influencing the efficiency of the valvular mechanism. Sometimes, cavities suddenly close because the bronchial obstruction becomes complete with subsequent absorption of the air in the cavity.

Maier<sup>8</sup> feels that there is a much better chance for closure of these cavities by *thoracoplasty* than by pneumothorax therapy. This may be due to immobility of the thoracic cage with resultant practical elimination of lung motion. This lack of motion may predispose to further obstruction of the bronchus. Often in such cases, cavity closure does not occur immediately after

thoracoplasty. But, after several months, the cavity may finally close and the sputum turn negative.

Suction (Monaldi) drainage of tension cavity by insertion of a catheter directly into it will invariably result in marked shrinkage in the cavity and lessening of sputum. However, even after several months of such drainage, there is always a great probability that the cavity will reopen as soon as the catheter is removed. In some cases, the Monaldi drainage has been used as a preliminary to thoracoplasty. Thus used, it reduces the size of the cavity and the amount of sputum and improves the patient's condition. However, the objection can always be raised that any patient with cavity closure under this combination of treatment might have had the same result with simple thoracoplasty.

Open cavitory drainage has sometimes been employed, particularly in cases with persistent residual cavitation following thoracoplasty. In Maier's experience, there has been considerable difficulty in obtaining healing of the chest wound after such a cavernostomy.

Maier<sup>8</sup> prefers lobectomy or pneumonectomy in selected cases with tension cavity. In sixteen cases of lobectomy for pulmonary tuberculosis, there was one death due to spread, three contralateral reactivations, two empyemata (with fistula). Two total pneumonectomies for tension cavity were followed by uneventful recovery.

**Drainage Treatment of Insufflated Cavities**—The term "insufflated cavity" has the same meaning as "tension cavity," "check-valve cavity," etc.

Eloesser, Rogers, and Shipman<sup>9</sup> prefer skin-flap drainage to the use of mechanical suction drainage with a catheter in the cavity because of the notorious technical difficulties connected with

such drainage continued over a long period of time. The skin-flap method of valvular drainage permits a certain amount of negative pressure to build up in the draining cavity (unless the bronchial fistula is very large) without the encumbrance of tubes, bottles, motors, etc. Once properly established, the flap is nearly foolproof in function.

The procedure may be a primary one to deflate a "tension cavity" or it may be secondary to an unsuccessful thoracoplasty. It is essential that the cavity be accurately localized and the route of access be carefully planned.

The routes may be anterior, lateral, or posterior. Anterior flaps are least desirable for technical reasons, because of the danger of subpectoral extension of infection, and because of lack of dependency of drainage.

The axillary route is preferable. It is applicable in cases of upper lobe cavitation. The base of the flap is placed over the rib to be resected. The flap is U-shaped, the free end pointing downward and the sides at right angles to the ribs. The flap consists of skin and subcutaneous tissue only. The rib overlying the cavity is resected along with its periosteum and any attached intercostal muscles; about 2 inches of rib is removed. The edges of the flap are sutured to the pleura by two sutures taken at sufficient distance from the tip of the flap to permit the tip to be inserted into the cavity at the second stage. The flap is then held in place by packing.

The procedure is done in two stages because there is danger of the flap becoming ulcerated and blown out of place by the intracavitary pressure, if the cavity is opened at this time. Two or three weeks later, the cavity is opened, preferably by a cautery, and the tip of the flap is placed into the cavity and held

there for a week or two by vaseline gauze packing.

Cavities in the apex of the lower lobe can only be drained by the posterior approach. The flap must be long because of the thickness of the chest wall. The base of the flap must lie superiorly and medially or it will be pulled away from the pleura by scapular movements. The cavity should not be opened until this flap is well adherent.

Tubes and packs should not be used since they defeat the purpose of the valve. The flap is left in place until the cavity is closed and until sputum and drainage are both negative for tubercle bacilli. After a year or more, the flap may be detached and sewed back into its original position.

Of twenty-four cases, twenty-three had flaps completed (one recovered after the first stage only), eighteen resulted in cavitary closure, three were unsatisfactory, two patients died of tuberculous meningitis.

It is now believed that these cavities persist first because of the bronchial valvular mechanism—the “intrinsic factor,” and second because of adherence to thickened pleura overlying them. This is called the “extrinsic factor.”

Therefore, Eloesser, Rogers, and Shipman<sup>9</sup> now believe that the following conditions should be met in performing flap drainage: (1) **Thoracoplasty** should have been done for upper lobe cavities (extrinsic factor dealt with); (2) **phrenic interruption** should have been done for lower lobe cavities (extrinsic factor dealt with); (3) the **residual cavity** should still be an **insufflated** one as shown by manometric reading (intrinsic factor still operative); and (4) the cavity should be opened in such a manner that the opening will remain adequate over a long period of time.

### Tracheobronchial Tuberculosis

At the present time there is no clear understanding of the reasons why 5 to 15 per cent of persons with pulmonary tuberculosis develop tuberculous bronchitis while the rest do not. The presence of this complication severely handicaps the clinician's therapeutic efforts and alters the prognosis unfavorably. Even more, the failure to recognize and allow for the presence of this complication is fraught with unexpected dangers. Yet, many phthisiologists are scarcely aware of the existence of this entity in clinical practice. This unawareness is aggravated by the inability of the bronchoscope to visualize the actual lesion in many cases because the disease may be limited to a nonvisualized portion of the bronchial system.

**Pathology**—Silverman,<sup>10</sup> in 110 autopsies on patients dying from pulmonary tuberculosis, found definite tuberculosis of the trachea or main bronchi in 66 instances (60 per cent). Many of the others presented diffuse reddening and edema of the mucosa, and some shallow ulcerations of a nonspecific character. These were not considered tuberculous endobronchitis in this statistical series, although that possibility cannot be completely ruled out. Gross ulcerations with tuberculous granulation tissue were more common than microscopic ulcerations. In some cases there was extensive associated fibrosis. This was capable of markedly narrowing or stenosing the smaller bronchi, but did not usually appreciably narrow the trachea. Complete occlusion due to healing by fibrosis was only seen in the small branches of the lobar bronchi. Lesser degrees of this were seen in the major bronchi. The high incidence of tracheobronchial disease in this series was doubtless due to the fact that these were studies of cases which had

died of tuberculosis and also to the care with which the search for the lesions was carried out. There seems to be no doubt that the severer the pulmonary disease, the greater is the tendency to development of tracheobronchial tuberculosis.

Meissner,<sup>11</sup> in reviewing sixty lungs or lobes resected for tuberculosis, found endobronchial tuberculosis in thirty-one cases. Here, too, the true incidence of the complication in pulmonary tuberculosis is not reflected since many of these cases were resected because of the endobronchial disease.

Meissner<sup>11</sup> has stressed that in many cases there is no actual ulceration of the mucosa, but merely submucosal tubercles plus some submucosal edema. The limitations of bronchoscopic study in such cases are obvious. In twenty-seven of the thirty-one cases with bronchial disease, the hilar lymph nodes revealed microscopic tubercles, but with minimal caseation. He has observed an apparent continuity of disease from the point nearest the hilum through the segmental bronchi to a parenchymal lesion.

Silverman<sup>10</sup> has shown that there is no direct correlation between the incidence of tracheobronchial and laryngeal tuberculosis.

**Pathogenesis** — In all cases Meissner<sup>11</sup> found the bronchial disease to be directly related to a parenchymal caseous focus (in twenty instances, this was an actual cavity) which permitted tubercle bacilli to drain over the affected bronchi. Silverman,<sup>10</sup> too, felt that endobronchial disease is practically always due to direct drainage of tubercle bacilli into the affected bronchi. This usually takes the form of direct surface implantation. Occasionally, a caseous focus such as a lymph node may break directly into a bronchus. Hematogenous implantation occasionally takes place, as in generalized miliary tuberculosis, Meiss-

ner feels that the lymphatics of the bronchial wall play an important rôle in the infection of the bronchi and in the spread of the disease.

**Radiology** — Birkelo and Poznak<sup>12</sup> have divided the radiological findings suggesting endobronchial disease into the direct radiological findings (more or less pathognomonic x-ray findings) and the "indirect" indications in which certain clinical observations are combined with certain otherwise negative radiological evidences to suggest the likelihood of endobronchial tuberculosis. They suggest the following classification:

Direct signs:

1. Atelectasis.
2. Sudden consolidation of a lobe under collapse.
3. Sudden spread of a lesion apparently controlled.
4. Blocked cavity.
5. Far advanced disease.

Indirect signs:

1. Hemoptysis of the milk or streaking type, without demonstrable x-ray findings.
2. Positive sputum without demonstrable cavity.
3. Persistent, nonproductive cough.

**Clinical Aspects**—Stone<sup>13</sup> feels that while the bronchoscope is only capable of revealing pathology in the larger bronchi, it is mainly with disease of the larger bronchi that we are concerned. Stenosis or obstruction of the larger bronchi is of serious clinical importance, but obstruction of the peripheral bronchi results in atelectasis of small segments of lung tissue and may have no clinical significance. Therefore, bronchoscopic examination is an extremely valuable method of diagnosing clinically important endobronchial disease. He draws his conclusions from a series of fifty proven cases bronchoscopically diagnosed. Thirty-six were females and fourteen males, about the expected ratio.



Stone<sup>13</sup> feels that the most significant symptom in these cases was a *localized* wheeze. This symptom was present in 62 per cent of cases. The 100 per cent collapsed lung or unexpandable "opaque" lung was next most prominent, being present in 40 per cent of the cases. Ballooning of the cavity under pneumothorax therapy or unexpected variations in size of the cavity under collapse therapy was noted in several cases. Pain or mild soreness in the substernal region was noted in 30 per cent of cases. Failure to close cavities or convert sputum with thoracoplasty, persistent cough, copious expectoration, hemoptysis, and sepsis were all noted in this series. Twelve per cent presented symptoms resembling tuberculous bronchiectasis. Anaerobic infection with abscess formation occurred in two cases following complete stenosis of a bronchus. In general, he feels that the symptoms and signs of clinically important endobronchial tuberculosis are those of partial atelectasis with resultant superimposed infection.

**Bronchoscopy**—Wilson<sup>14</sup> divides the stages of tuberculous bronchitis as follows: (1) Submucosal infiltration; (2) ulceration and hyperplastic changes; (3) healing. These stages frequently coexist.

In stage 1, the bronchoscopist may see granular and reddened mucosa, particularly around one of the bronchial orifices, usually the posterior half of its circumference. The bronchial wall is indurated and edematous so that the cartilaginous rings do not stand out normally or may be entirely obliterated. Submucosal nodulation, representing tubercles, may or may not be seen. Some degree of narrowing of the main bronchus is usually present but as a rule the main bronchus has an adequate airway. Such a process may be localized to the bronchial orifice or may extend to in-

volve the entire main bronchus and extend into the trachea.

Stage 2 may appear at any time in the course of stage 1. Ulceration and granulation tissue become evident. Hyperplastic changes in the bronchial wall become more marked and the cartilages may become involved; this is evidenced by increased mobility of the bronchial wall. Ulceration may occur early or late in the course of a case of pulmonary tuberculosis and at any point along the involved portion of the bronchus. The ulcers have irregular edges and the base is often covered with grayish exudate.

Stage 3 usually appears insidiously during stage 1 or 2. It often takes place in portions of the bronchial tree while the inflammatory process continues extending in other portions. The submucosal types of involvement show progressively less inflammatory reaction and edema, and the mucosa becomes less granular and friable. Isolated ulcers heal with very little evidence of scarring. Where tissue destruction has been marked, stenosis will eventually appear as a result of fibrosis. The degree of stenosis will depend upon the extent of tissue destruction and its occurrence can usually be predicted by the bronchoscopist by the character of the preexisting lesion.

For unexplained reasons, the ultimate stenoses tend to involve some portions of the bronchial tree much more often than others. In thirty-six consecutive cases of stenosis, twenty, or 55.5 per cent, involved the left main bronchus and eleven, or 30.5 per cent, involved the orifice of the right upper lobe. Presumably these stenoses occur at the point of maximum destruction of the bronchial wall and perhaps have something to do with the lymphatic drainage of the bronchial wall itself.

Wilson<sup>14</sup> considers that all cases of pulmonary tuberculosis should be bronchoscoped, but when such a routine cannot be established, the following indications must be recognized for the procedure:

**A. Clinical indications:**

1. Unilateral wheeze.
2. Positive sputum without evidence of parenchymal source.
3. Positive sputum with apparently controlled parenchymal disease.
4. Severe symptoms (cough, difficulty in raising sputum, dyspnea, and cyanosis) without evident cause in the parenchyma.
5. Evidence of intermittent retention of secretions, such as variation in the amount of sputum and the occurrence of fever.
6. Prolonged fever following thoracoplasty.

**B. Roentgenological indications:**

1. Mediastinal shift with or without elevation of diaphragm.
2. "Hilar flare."
3. Opaque lesions of lobular, lobar, or multilobar distribution. (Opaque lesion is used in preference to the term "atelectasis"). These may appear suddenly following collapse therapy.
4. Basal tuberculosis.
5. Certain types of cavity:
  - a. Those with thin walls and fluid levels.
  - b. Those that fluctuate in size.
6. Widespread parenchymal disease without evident parenchymal source.
7. Obstructive emphysema.

**C. Contraindications to bronchoscopy are:**

1. Terminal phase of the disease.
2. Pulmonary hemorrhage.
3. Acute respiratory infection.
4. Tuberculous laryngitis. If this involvement is of the ulcerative type, bronchoscopy should not be done except for an extreme emergency. If the involvement is of the submucosal type, bronchoscopy may be performed if it can be done without trauma.

**Treatment**—This is not entirely satisfactory at present. Stone feels that various methods of treatment must be

applied and followed up for years before definite conclusions can be drawn about this disease. In general, there is a tendency for the bronchial disease to subside if the parenchymal disease is controlled. This would be expected on the basis of Silverman's concept that bronchial disease is mainly caused by surface contact of infected secretions. However, Wilson has shown that once endobronchial disease is well established, it becomes to a considerable extent independent of its parent caseous focus and is then self-propagative. Furthermore, the usual measures employed in treating parenchymal lesions are collapse measures. These measures, especially pneumothorax, tend to aggravate any impairment of bronchial drainage and may change a partially stenotic lesion into an acutely stenotic one. This is the explanation of the phenomenon of "opaque" lobe or lung (atelectatic lung with varying amount of retention and infection) which may suddenly occur after the induction of a pneumothorax. It is common enough to justify Wilson's contention that no case should be subjected to collapse therapy until bronchoscopy has been performed to at least rule out high grades of ulceration or stenosis of the larger bronchi. However, there is a great difference in the various forms of collapse therapy in bronchial stenosis. While phrenic paralysis and especially pneumothorax are definitely contraindicated in any case with high-grade bronchial stenosis, thoracoplasty may usually be tried with impunity unless there is already a complete stenosis.

Wilson<sup>14</sup> strongly advises the topical application of 30 per cent *silver nitrate* via bronchoscope in the ulcerative and ulcerohyperplastic types. He feels that such treatments must be repeated at least once every two weeks.

Conservative management may be followed by uneventful healing in cases of submucosal involvement or limited ulceration providing the parenchymal disease is under control. *X-ray therapy* has been recommended by some.

Overholt and Wilson<sup>15</sup> have pointed out that while complete thoracoplasty is effective in a considerable number of cases of marked bronchial stenosis, it is really less valuable than superficially apparent since it is rarely applied in cases progressing rapidly downhill. Only those which weather the storm and become stabilized are subjected to thoracoplasty. Tension cavities, basal disease, and widespread active disease are common with bronchial involvement, and yet these conditions are notorious for their poor response to thoracoplasty. Therefore, these authors have been resorting to lobectomy and pneumonectomy in an increasing number of cases. They report thirty cases of tracheobronchial tuberculosis operated between 1934 and 1944. Twelve were considered as desperate or last resort cases and eighteen were considered reasonable risks. The sex ratio was four females to one male. Twenty-four had stenotic bronchial lesions, eleven with associated ulceration. Five had ulcerative lesions, and one had a submucosal lesion with marked edema.

Of nineteen cases operated between January, 1942, and January, 1944, five operative deaths occurred, four of these being among the seven desperate risk cases, making an overall mortality of 26.3 per cent. The reasonable risks resulted in a mortality of 8.5 per cent, while the desperate risks resulted in a 57.1 per cent mortality. Contralateral spreads occurred in 15.8 per cent of the cases. Bronchial stump ulcers occurred in 21 per cent of cases. Bronchial fistula occurred in 5.2 per cent of cases, and empyema occurred in 10.4 per cent.

Overholt and Wilson<sup>15</sup> stress that resection is not to be considered as a competitive but as a supplementary type of therapy to other longer established methods of treatment of bronchial tuberculosis.

**Pulmonary Resection for Tuberculosis Symposium** — The symposium presented at the twenty-fifth annual meeting of the American Association for Thoracic Surgery, Chicago, May 5, 1944, upon surgical experiences with lobectomy and pneumonectomy for pulmonary tuberculosis is the most up-to-date and authoritative dissertation upon the subject, a most timely one. Since collapse therapy is only effective in approximately three fourths of the cases in which it is persistently applied, and since the limitations of drainage procedures are narrow, excision of the active focus in localized pulmonary tuberculosis is logical and will undoubtedly be exploited more freely when the surgical indications and management are better understood. Many clinical observations and deductions have been recorded in this series of papers, the full importance of which has not been thoroughly appreciated as yet. Nevertheless since, during the past eighteen months the author, who only took part in the open discussion of this symposium, has had an opportunity to visit and communicate with some of these same authors, and has operated upon some forty-odd more cases, he will attempt to emphasize such of these observations as now seem most important to him.

Dolley<sup>16</sup> has stressed that new procedures in thoracic surgery have uniformly followed a regular pattern, and that this certainly has been true in resection for pulmonary tuberculosis. He points out that first the procedure is announced and recommended for a particular condition along with the presentation of an inadequate series of cases, recently done

and with unconvincing conclusions. Skepticism is manifested by the audience and such clinical trial as is performed by them is limited and halfhearted. The selection of cases is poor and results are discouraging. Subsequently disasters are reported and the operation is condemned. After months or years, several independent workers suddenly report larger series of cases, better selected, and with experience in surgical technic and management modified by the previous disasters and unsatisfactory results of early cases. A wave of often violent enthusiasm follows and the operation takes precedence over less radical and more dependable procedures. Finally, with greater experience, proper evaluation of the procedure permits standardization of indications, technic, and management, and the procedure is placed in its proper niche. Dolly feels that resection for tuberculosis is now in the enthusiastic stage.

James<sup>17</sup> has reported two deaths following seventeen lobectomies for tuberculosis and three deaths following fifteen total pneumonectomies. Three additional cases among the pneumonectomies are in poor general condition and may eventually succumb. Seven of the first group and twelve of the latter group did not have demonstrable cavities, but rather had bronchiectasis, bronchial stenosis, tuberculous bronchitis, or (one case) tuberculoma. All but one of the cavitory cases had already been subjected to apparently adequate extensive collapse therapy without cavity closure.

James<sup>17</sup> feels that one should not divide a bronchus through an area of active tuberculous bronchitis. He has stressed that if there is even moderate narrowing of a main bronchus, it is necessary to perform a total pneumonectomy rather than a lobectomy for the cavitory lesion. He utilizes the lateral operative position and a posterolateral

approach without removal of a rib. The bronchus has been divided as proximally as possible and closed by a running end suture of chromic catgut with or without reinforcing silk sutures. The stump is covered with pleura or other tissue. He does not perform routine postoperative thoracoplasty.

It must be observed that the series of cases reported by this author is essentially one of stabilized chronic, often far advanced, pulmonary or bronchial tuberculosis in which prolonged observation and sanatorium or collapse treatment had already been applied.

On the other hand, Maier and Klopstock<sup>18</sup> have reported upon sixteen cases of lobectomy in earlier types of pulmonary tuberculosis. None of these have had previous thoracoplasty and none had tuberculous bronchiectasis. All were in good general condition, even though several showed considerable evidence of activity as shown by the sedimentation test, slight fever, and elevated pulse rate. Only one had a large amount of sputum (and this case died of a fatal contralateral operative tuberculous spread).

The posterolateral approach with resection of one rib was employed routinely. Extrapleural dissection was employed wherever cavities came close to the chest wall and wherever the lung was extremely adherent to the chest wall. An attempt was made to ligate the bronchus soon after opening the thorax in order to prevent contralateral expression of infected secretions. For technical reasons this cannot always be readily done. Closure of the bronchus was accomplished by interrupted fine silk end sutures, and the stump was covered by a flap of pleura. Drainage is employed for twenty-four to forty-eight hours to favor reexpansion of the remaining lobe, which is freely mobilized. The phrenic nerve is crushed in most cases to lessen the size

of the pleural space to be obliterated by the expanding lung. Anesthesia is given through a simple endotracheal catheter with or without a cuff. Cyclopropane or a gas-oxygen-ether sequence is used. The anesthetist is charged with the responsibility of preventing contralateral expression of secretions and thus of bronchiogenic spread. (The editor considers this an unfair responsibility, particularly in cases with much sputum.)

Ten of the patients had an uneventful and uncomplicated postoperative course. In three there was radiographic evidence of contralateral flare-up of preexisting tuberculous disease. Since the process promptly improved, these lesions were not considered to be tuberculous spread. One patient developed an apical staphylococcic empyema with bronchial fistula, and one a pure tuberculous empyema with fistula. Death resulted in one case from a tuberculous contralateral spread. This patient had had a large tension cavity with a fluid level. The patient was fairly toxic.

Maier and Klopstock raise the question of the advisability of routine limited thoracoplasty after upper lobectomy to prevent hyperinflation of the remaining lobes. They feel that the passage of some years will be necessary before a definite decision can be reached on this subject.

Chamberlain,<sup>19</sup> on the other hand, feels that the reduction of pulmonary function which occurs following lobectomy with overstretching of the remaining lobes is much greater than that following selective thoracoplasty. He has shown this to be true in a small series of cases by bronchspirometric studies. He also points out that in forty-six cases subjected to apical or upper lobe thoracoplasties (six ribs or less), the sputum was converted in 80 per cent of cases. There was only one death in the

series. He, therefore, feels that thoracoplasty should be done first, and lobectomy reserved for the case in which it fails. He also points out that even cases of tuberculous bronchiectasis can be converted in many cases by especially good thoracoplastic collapse. He quotes Alexander (1942), Tuttle (1942), and Chamberlain and Gordon (1942) to show that thoracoplasty is safe and effective in many cases of endobronchial tuberculosis including stenosis.

Overholt and Wilson<sup>20</sup> have accepted patients for resection on much wider indications than any of the other authors. They take cases which fall into the "desperate risk" classification (Alexander's "Collapse Therapy of Pulmonary Tuberculosis," 1937) as well as all other varieties of cases recommended for resection. They also perform resection as an elective procedure in certain cases which might well respond to thoracoplasty, notably lower lobe cavities, large or hilar cavities, tension cavities, and even active tuberculous disease in diabetics.

These authors stress the absolute necessity of the individual ligation technic in these cases. They also feel that any tuberculous flare-up in the same or opposite lung must be considered as a bronchiogenic spread until proven otherwise. Since such a thing can only be proven if the flare-up promptly subsides, they have at least 11.1 per cent of listed contralateral and 4.4 per cent of ipsilateral spreads in forty-five cases done between 1942 and 1944. These cases were all operated by the posterolateral approach with resection of one rib. Forty consecutive resections done in the months preceding December 15, 1945, were operated in a face-down position which prevents, as far as possible by gravity, expression of infective secretions from the infected into the noninfected lung. In this series, only one contralateral

spread occurred. These results seem to corroborate their theory that the preponderance of contralateral exacerbations are really tuberculous spreads by the bronchiogenic route.

The editor,<sup>21</sup> too, has felt that spreads and exacerbations are due to direct expression of secretions from the diseased into the normal lobes during the manipulations of surgery, and has attempted to control this factor by endobronchial packing and endobronchial anesthesia tubes in which are incorporated direct bronchoscopic types of visual system. The anterior (Rienhoff) approach for upper lobectomies and total pneumonectomies is also useful for the purpose of preventing bronchiogenic spread providing that the operated side is kept lower than the unoperated, and provided that a moderate Trendelenberg position is employed. Unfortunately, the exposure afforded by this incision is not large. It seems to the editor that it is possible to utilize gravity to prevent bronchiogenic spread, this being preferable to difficult and time-consuming endobronchial manipulations which traumatize the bronchial mucosa and cause a thin sanguino-mucoid discharge. Such a secretion might well carry bacteria into other lobes during the postoperative period unless the patient is able to cough it up.

### Benign Tumors of the Lung

The so-called "adenoma of the bronchus" is the second most common primary tumor of the lung, being about one tenth as common as carcinoma. These tumors are slow growing and usually arise in the major bronchial divisions as papillary or sessile growths. There is frequently a considerable extrabronchial portion. They tend to appear in young females. Sixteen of the twenty cases reported by Jackson, Konzelmann, and

Norris<sup>22</sup> were females, and none were over forty-five years of age.

Jackson, Konzelmann, and Norris believe that bronchial adenomas may infiltrate the wall of the bronchus and any tissue which comes in their path just as a basal-cell carcinoma of the skin might do. However, they feel that such infiltration is sufficiently infrequent, and limited when it does occur, so that endobronchial removal is justified where it can be done, admitting that complete removal by this means is often not possible, and that, obviously, incompletely removed tumors will recur. Furthermore, they feel that repeated removal does not cause more rapid growth or alter the behavior of the remaining cells. They believe that lymph or blood stream metastasis is extremely rare, and that they have met no true carcinomas of the lung which started as adenomas.

Graham and Womack,<sup>23</sup> on the other hand, believe that these tumors are all potentially malignant, and cite several indisputable cases from their own clinic in which both the lymph node and distant (liver) metastases have occurred. Further, they utilize the literature to show that other such cases have been reported. They report one case of their own and one from the literature in which bronchoscopic removal of an apparently typical adenoma was followed by great improvement for several years, and then by recurrence and death from carcinoma of the lung. Unless it can be shown that the original diagnosis is wrong in these two cases, they would seem to be sufficient to prove Graham and Womack's viewpoint.

Chamberlain and Gordon<sup>24</sup> report ten cases in which seven were cured by pulmonary resection, and two died subsequent to bronchoscopy. One of these deaths was due to asphyxia from an intrabronchial blood clot, and one to

asphyxia from a pedunculated portion of the tumor. Interestingly enough, this last case had been bronchoscoped five years previously and the slides from the biopsy specimen were available for comparison with the slides from the autopsy specimen. The biopsy had been diagnosed by Konzelmann as from an adenocarcinoma grade two, but the specimen actually seemed typically adenomatous except in one area where it suggested malignancy. The autopsy specimen revealed that marked histologic transition had taken place, the pattern being predominantly malignant.

Chamberlain and Gordon<sup>24</sup> point out that in every one of their cases there was marked extrabronchial extension of the tumor so that complete removal by bronchoscopy would have been impossible. They also point out that even after successful maintenance of an airway by repeated bronchoscopic removal, there is progressive narrowing of the bronchial lumen over the years due to either intramural or extrabronchial growth (Clerf and Bucher, 1942).

The symptoms of these tumors are cough and hemoptysis due to irritation and bleeding from the local lesion; wheezing and dyspnea due to unilateral partial bronchial obstruction, and those associated with atelectasis, pneumonitis, bronchiectasis, abscess, or even empyema after more complete obstruction and infection are established.

**Treatment**—Once this latter group of complications has become permanent, only pulmonary *resection* can relieve the symptoms and none of the authorities question the indications. Graham and Womack prefer total pneumonectomy because of greater completeness of lymph node extirpation. Chamberlain and Gordon<sup>24</sup> prefer lobectomy where feasible.

Jackson, Konzelmann, and Norris<sup>22</sup> feel that bronchoscopic removal is indicated as long as the biopsy indicates a benign lesion providing irreparable distal suppuration has not become superimposed. They feel that the risk of endoscopic procedures in skilled hands is slight.

Graham and Womack,<sup>23</sup> while accepting bronchoscopic treatment as a necessary palliative in certain poor risk cases, and while admitting it may sometimes be a valuable part of preoperative preparation, feel that the tumor is at least potentially malignant, and point out that the usual extrabronchial portion of the tumor cannot be removed endoscopically. Since there is frequently doubt from the biopsy studies whether the tumor is actually malignant at that time, resection is the safest procedure. They suggest that the extreme rarity of adenoma of the bronchus in persons past middle life may be due to the fact that they may all by then have undergone metaplasia into their malignant counterparts.

### Hamartoma

McDonald, Harrington, and Claggett<sup>25</sup> report upon twenty-three cases of hamartoma of the lung. They refer to those benign tumors which are predominantly composed of cartilage, but also contain epithelial elements and frequently mucous cysts. This is a change from the original meaning of the term "hamartoma," used by Albrecht (1904) to describe a tumor of a tissue in which all the normal elements of that tissue are present but in a scrambled fashion. While such a definition would doubtless include the "hamartoma" of McDonald, Harrington, and Claggett, it would also include any mixed cell tumor. Womack and Graham (1938) have already applied the term in that sense to "adenoma" of the bronchus.

Twenty cases were found at necropsy in 7972 consecutive cases—an incidence of 0.25 per cent. The other three were surgical cases, two of which were picked up during routine x-rays of the chest, and one who really had symptoms (dyspnea and burning feeling in right anterior chest).

These tumors are usually found well out in the parenchyma of the lung, not associated with a bronchus. They are frequently subpleural and vary from a diameter of less than 1 cm. to one encroaching upon the size of the thorax. They may become calcified or ossified. They apparently have no age or sex predilec-

### Pulmonary Lymphatic Regions (ROUVIERE)

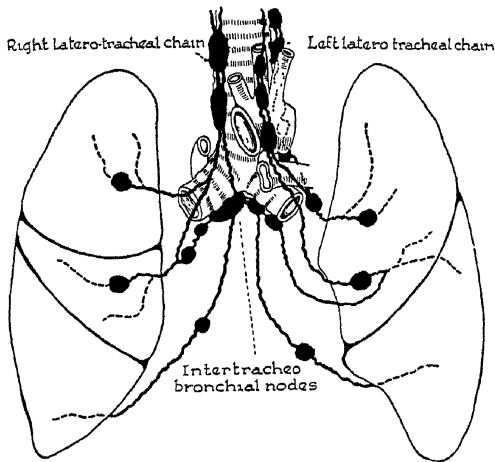


Fig. 3.

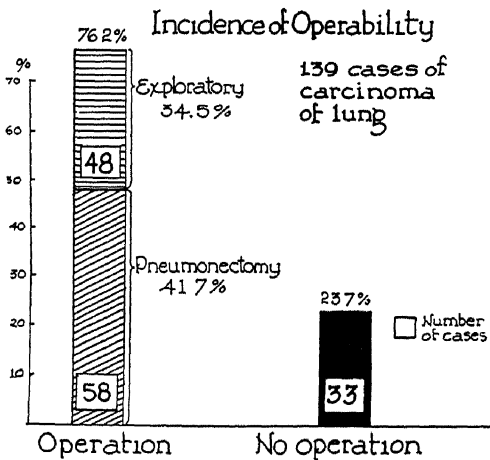


Fig. 5.

### Results in 190 cases-Carcinoma of Lung Diagnosed Clinically

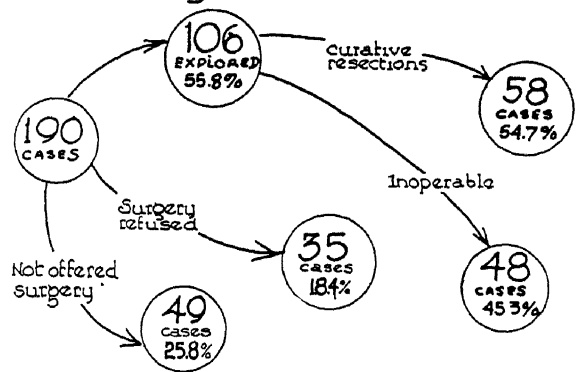


Fig. 4.

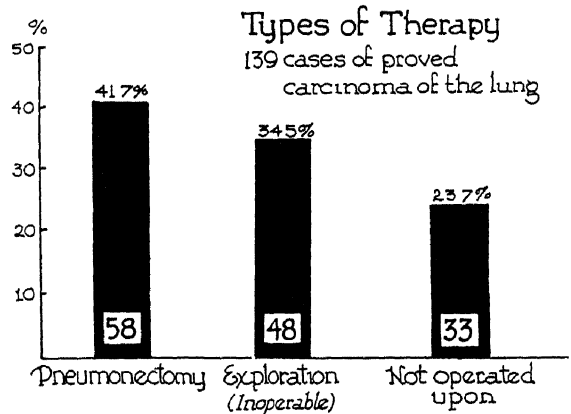


Fig. 6.

Fig. 3—(After Ochsner, A. and DeBakey, M.: Jour. Thor. Surg. 11: 357, 1942). Diagrammatic representation of lymphatic drainage of the lungs (after Rouviere). (Ochsner, A., Dixon, J. L., DeBakey, M.: Clinics 3: 1187 (Feb.) 1945.)

Fig. 4—Graphic representation of results in authors' 190 cases of carcinoma of the lung diagnosed clinically. (Ochsner, A., Dixon, J. L., DeBakey, M.: Clinics 3: 1187 (Feb.) 1945.)

Fig. 5—Graphic representation of incidence of operability in authors' 139 cases of proved carcinoma of the lung. (Ochsner, A., Dixon, J. L., DeBakey, M.: Clinics 3: 1187 (Feb.) 1945.)

Fig. 6—Graphic representation of types of therapy in authors' 139 cases of proved carcinoma of the lung. (Ochsner, A., Dixon, J. L., DeBakey, M.: Clinics 3: 1187 (Feb.) 1945.)



tion. They will probably be found more frequently now that mass x-ray surveys are being carried out.

The tumor is slow growing and strictly benign. It should be considered in the differential diagnosis of every solitary lung lesion. Treatment recommended is local resection, perhaps up to a lobectomy. Frozen sections may be made at operation to determine whether more extensive resection is necessary.

**Cylindroma of the Bronchus**—MacDonald, Moersch, and Tinney<sup>26</sup> re-

atelectasis, pneumonitis, bronchiectasis, or lung abscess. They are more likely than adenomas to involve the trachea. They are moderately radiosensitive.

Bronchoscopically and clinically, they resemble adenomas.

Treatment is along the same lines as that of adenoma, either by bronchoscopy or pulmonary resection.

### Primary Bronchiogenic Carcinoma

The incidence of primary malignancy of the lung is probably second only to

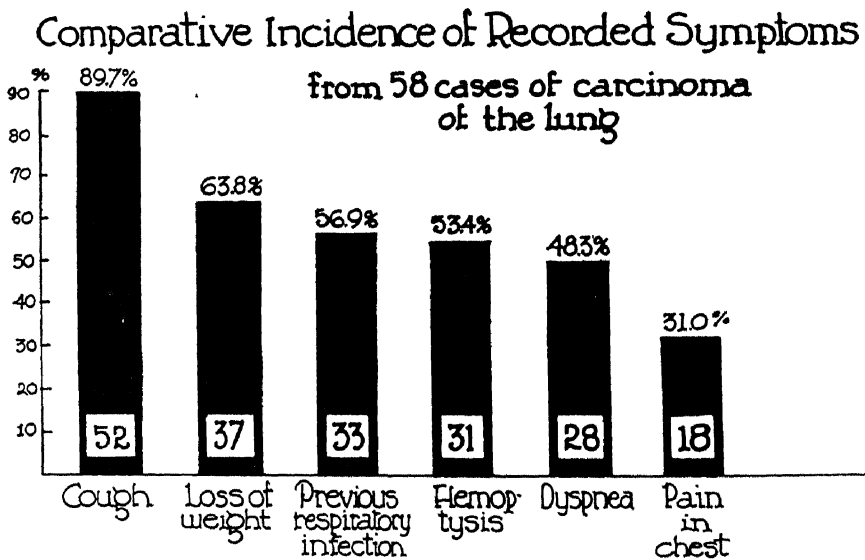


Fig. 7—Graphic representation of comparative incidence of recorded symptoms in 58 of authors' cases of carcinoma of the lung. (Ochsner, A., Dixon, J. L., DeBakey, M.: *Clinics* 3: 1187 (Feb.) 1945.)

port six cases of "cylindroma" appearing at the Mayo Clinic. These tumors in many respects resemble the so-called "adenoma" of the bronchus but the authors believe them to more closely simulate "mixed-cell" tumors such as seen in the parotid. The main point of differentiation is that the cylindroma produces a mucoid secretion while adenomas do not.

These tumors are only slightly malignant and do not ordinarily metastasize, although they may invade locally. They produce bronchial obstruction and distal

malignancy of the stomach. It makes up about 10 per cent of all malignancies and causes 1 per cent of all deaths. With few exceptions it occurs in older persons, only 10 to 20 per cent occurring in patients under forty years of age. It is occasionally seen in children, however. It is found four to ten times more commonly in males than in females. Ochsner, Dixon, and DeBakey<sup>27</sup> emphasize that the probable increase in incidence of bronchiogenic tumors may be related to the use of tobacco (smoking). After all, tobacco smoke is always inhaled to some

extent in smoking, and the smoke has been shown to contain carcinogenic substances. These substances can produce basal cell carcinoma of the skin in mice if repeatedly and persistently applied.

The disease is almost entirely a disease of the bronchi, but rarely may begin in the alveoli. Most of these tumors probably begin in the basal layer of the bronchial mucosa. They appear to arise most frequently at the junction of the bronchial branch with its parent stem (Barnard, 1943). The mucosa over the lesion is intact except for changes in color (gray or whitish pink).

Ochsner, Dixon, and DeBakey prefer Halpert's (1939) classification of these tumors: (1) "Reserve cell" carcinoma; (2) cylindric cell carcinoma, and (3) squamous cell carcinoma. They first produce solid masses of cells growing in no particular form. They second form tubular or acinar structures. Squamous cell carcinomas characteristically tend to keratinization and pearl formation. At the Charity Hospital in New Orleans,<sup>27</sup> the bronchiogenic carcinomas were found in these three classifications in the ratio of 30-20-50, respectively.

The authors feel that generally these tumors grow slowly and metastasize late. At least 10 per cent show no metastasis even at autopsy.

Because of the advanced stage at which the diagnosis is usually made, most cases are found to be not surgically curable. Of 190 diagnosed cases, the authors performed exploratory operations in only 106 cases (55.8 per cent). Thirty-five (18.4 per cent) patients refused. Fifty-eight (54.7 per cent) of the operated cases were found operable and pneumonectomies were performed. This amounted to 30.5 per cent of all diagnosed cases. Of these 58 cases, metastasis to the mediastinal nodes was found in 33 (56.9 per cent), suspicion

of metastasis existed in 11 (18.9 per cent) cases, and no metastases were found in 14 (24.1 per cent) cases. (Figs. 3, 4, 5, 6, 7, 8.)

The clinical picture is frequently insidious, comprising various combinations of cough, sputum, hemoptysis, dyspnea, stridor or wheezing, pain, secondary

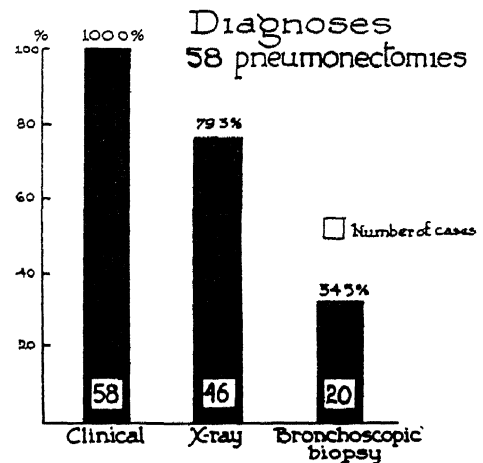


Fig. 8—Graphic representation of diagnosis in authors' 58 pneumonectomies. (Ochsner, A., Dixon, J. L., DeBakey, M.: *Clinics* 3: 1187 (Feb.) 1945.)

anemia, loss of weight, chills, fever, weakness, anorexia, and evidences of metastasis.

The diagnosis is most easily made by being constantly aware of its possible occurrence. It must be expected in every male patient forty years or older with cough, hemoptysis, or thoracic discomfort. X-ray may show the shadow of the tumor itself, a shadow due to enlarged mediastinal nodes, or one due to atelectatic lung tissue with or without distal infection. The authors were able to make a correct diagnosis radiographically in 79.3 per cent of cases. Bronchography and tonography are valuable auxiliary radiographic methods.

Bronchoscopic visualization and biopsy is perhaps the best diagnostic method. It should be theoretically possible to obtain a positive biopsy in about 70 per

cent of cases, because that is the incidence of hilar involvement. Unfortunately, visualization of the upper lobe bronchi is difficult.

The finding of malignant cells in expectorated material is of great diagnostic value, some authors reporting positive findings in 60 to 80 per cent of cases. It is, as would be expected, easier to find such cells in late cases rather than early. However, some early cases do show malignant cells in the sputum.

tumor, upon the presence or amount of infection, and the amount of bronchial obstruction present. Complete cures are extremely doubtful and rare.

**Surgical extirpation** of the entire involved lung is the only curative treatment. All involved hilar and mediastinal nodes must be removed at the same time. Pneumonectomy has been performed in a man seventy-two years of age. Pre-operative *pneumothorax* is considered valuable, both diagnostically and to pre-

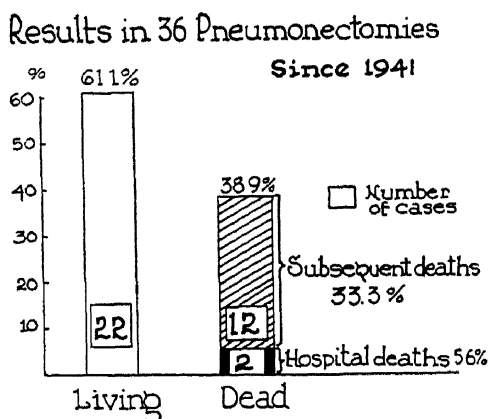


Fig. 9.

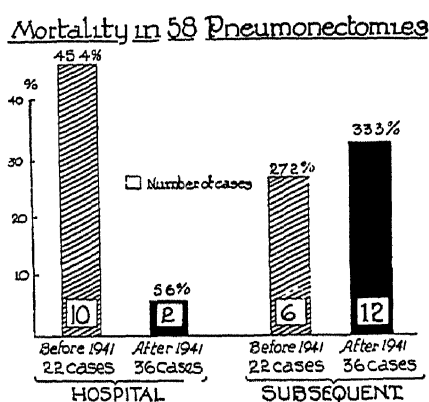


Fig. 10.

Fig. 9—Graphic representation of results in authors' 36 pneumonectomies since 1941. (Ochsner, A., Dixon, J. L., DeBaKey, M.: Clinics 3: 1187 (Feb.) 1945.)

Fig. 10—Graphic representation of mortality in authors' 58 pneumonectomies. (Ochsner, A., Dixon, J. L., DeBaKey, M.: Clinics 3: 1187 (Feb.) 1945.)

Aspiration biopsy is only recommended for diagnosis in the case not suitable for pulmonary resection since there is some danger of implanting malignant cells in the chest wall or pleura.

**Thoracic exploration** is justified in every possibly curable case in which the diagnosis cannot otherwise be made. At that time, a decision as to operability can be made and, if feasible, a pneumonectomy may be carried out immediately. Only by exploratory thoracotomy can an accurate diagnosis be made in many early curable tumors.

**Radiation therapy** may be employed in the inoperable case, good or poor results depending upon the nature of the

pare the patient for the loss of one lung and its contained circulation.

The anterior operative approach through the third interspace as recommended by Rienhoff is considered preferable in resections for malignancy. In the presence of extensive pleural adhesions, the posterolateral approach is more advantageous. Of fifty-eight pneumonectomies, sixteen (27.6 per cent) died before leaving the hospital. This includes the earliest operative cases done before the development of a modern technic. (See Figs. 9, 10, 11, 12.)

Postoperative bronchoscopy is routine to remove blood and mucus from the tracheobronchial tree.

### Carcinoma in the Bronchial Wall—

Griess, McDonald, and Clagett<sup>28</sup> found that extension of bronchiogenic carcinomas within the proximal bronchial wall varied considerably. In some cases, there was practically no extension beyond the visible margin of the tumor. In others, it extended as far as 20 mm. proximally. Adenocarcinomas appeared to extend farther than squamous cell carcinomas. The authors recommend division of the bronchus at least 1.5 cm.

malities are present may sometimes be successfully subjected to ductal ligation.

If the ductus fails to close soon after birth, the condition is essentially that of a large arteriovenous aneurysm, since the blood passes from the aorta directly into the pulmonary artery which is a carrier of venous blood.

Nixon<sup>29</sup> believes that Gross<sup>30</sup> has described the three most probable reasons for persistent patency of the ductus: (1) If the ductus does not enter the

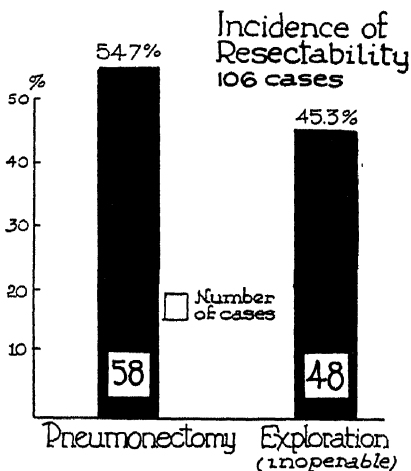


Fig. 11.

Fig. 11—Graphic representation of incidence of resectability in 106 of authors' cases. (Ochsner, A., Dixon, J. L., DeBakey, M.: Clinics 3:1187 (Feb.) 1945.)

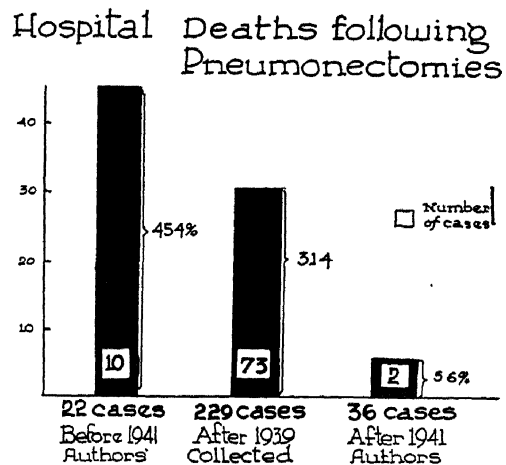


Fig. 12.

Fig. 12—Graphic representation of hospital deaths following pneumonectomies. (Ochsner, A., Dixon, J. L., DeBakey, M.: Clinics 3:1187 (Feb.) 1945.)

proximal to the lesion in squamous cell carcinoma, and at least 2 cm. in adenocarcinoma, if anatomically feasible.

### Surgical Closure of the Ductus Arteriosus

Since 1928, when Gross first successfully ligated a patent ductus arteriosus, great interest has been aroused in this subject. More recently the field of applicability has been extended since it has been found that the operation may be curative in cases of *Streptococcus viridans* infection of the ductus. Even cases in which other congenital cardiac abnor-

aortic arch at the normal acute angle but rather at a right angle or even at an obtuse angle, the ductus becomes more and more exposed to intra-aortic pressure and thus more and more liable to remain patent; (2) the second possibility is a defect in the elastic fiber of the media, decreasing the contractility of the ductus; (3) the third possibility is a deficient neurovascular tonus. Of course, there are certain other congenital defects which require the compensating effect of a patent ductus arteriosus for the maintenance of life, and they tend to cause its persistence by virtue of the

greatly increased blood flow through it.

The hazards of an uncomplicated patent ductus arteriosus are related, first, to great overwork of the heart with its tendency to congestive failure, and second, the risk of acquiring a subacute bacterial infection upon the walls of the abnormal channel. That the total risk of such a defect is considerable, was shown by Abbott in 1937 in whose ninety-two

about 25 per cent. Other complications are aneurysm of the ductus, rupture of the ductus, and possible retrograde thrombosis and embolization.

The diagnosis is seldom made until the child is several years old. Shortness of breath and palpitation are the earliest symptoms. The patient may or may not be undernourished or underdeveloped. Cyanosis is not present except as a

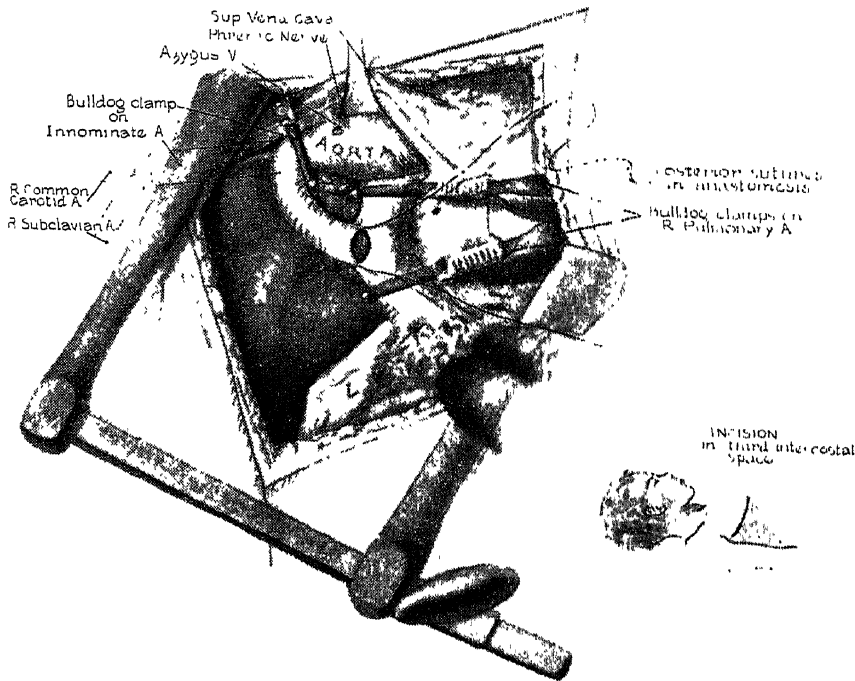


Fig. 13—General exposure of the operative field on the right side. The end of the innominate artery is being anastomosed to the side of the right pulmonary artery. The posterior row of sutures is complete. The anterior row has not been inserted. (Blalock, A. and Taussig, H. B.: J. A. M. A. 128: 190 (May 19) 1945.)

cases the mean age at death was twenty-four years. In eighty cases reviewed by Jones, Dolley, and Bullock in 1940, all over three years of age at death; 14 per cent died of their heart lesion by fourteen years of age; 50 per cent died of their heart lesion by thirty years of age, and 71 per cent died of their heart lesion by forty-one years of age.

Gross in 1940, and Abbott in 1936, have computed the risk of subacute bacterial endarteritis in these cases to be

terminal feature. On physical examination, the heart is found enlarged and there is almost invariably a "machine-like" murmur with systolic accentuation heard best over the second or third interspace to the left of the sternum. There is usually a palpable thrill associated with the murmur. The blood pressure tends to be of the Corrigan type, but usually the systolic pressure is low or low normal. The electrocardiogram is usually normal. X-ray shows enlarge-

ment of the heart, a large pulmonary conus, and congestion of the opposite lung and hilus.

The risk of the condition is such that every case should be subjected to ligation. There are two definite contra-

ready spread to the endocardium, aorta, mitral valve, or aortic valve.

Nixon<sup>29</sup> employs the following surgical technic:

The incision begins at the lateral border of the sternum and extends laterally for five to

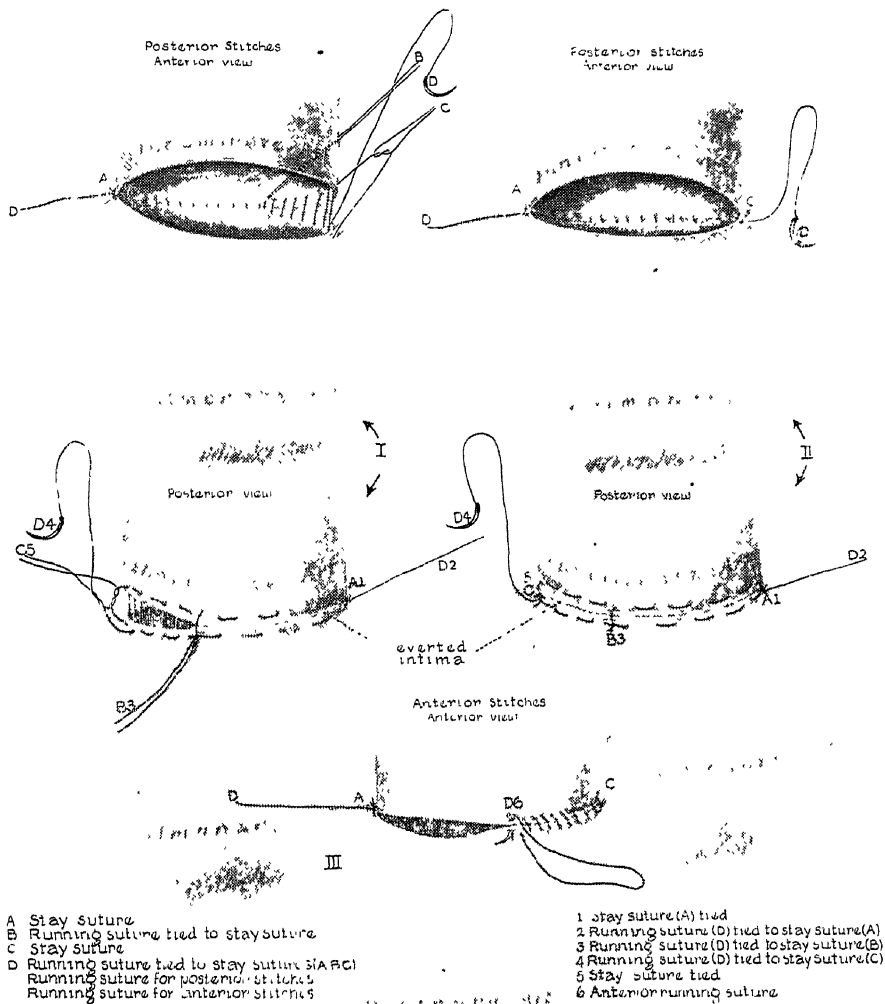


Fig. 14—Details of the method by which the end of a systemic artery is anastomosed to the side of one of the pulmonary arteries. (Blalock, A. and Taussig, H. B.: J. A. M. A. 128: 191 (May 19) 1945.)

indications (Touff, 1942) to operations. First are those cases in which the ductus is known to be an essential compensating mechanism for other congenital defects. Second are those where there is strong evidence that vegetations in subacute bacterial endarteritis have al-

six inches over the second interspace. The pleura is entered through this interspace. The mediastinal pleura is incised upward from the "sentinel" lymph node found at the superior border of the lung root. The aorta is dissected free in this area, remembering that the aorta is tough-walled while the ductus is fragile and easily torn. The vagus nerve is identified and

traced to its recurrent branch which runs medially under the ductus. The area of maximal thrill (representing the ductus) is sought by palpation. The ductus is gently mobilized and doubly ligated, using number 8 braided silk.

Usually, the machine murmur and thrill disappear with the ligation of the duct. However, a residual murmur may sometimes be present. The heart action immediately becomes more normal and the diastolic blood pressure rises. Gain in nourishment and weight may be dramatic.

The mortality of subacute bacterial endarteritis in medically treated cases is

### Congenital Heart Disease

Blalock and Taussig<sup>31</sup> have for the first time presented a surgical method of improving the efficiency of the cardio-respiratory system in certain cases of congenital cardiac malformation. Cases suitable for such manipulation are those with cyanosis due to pulmonary stenosis or atresia, or an equivalent diminution in the amount of pulmonary circulation, such as may be seen in truncus arteriosus where only bronchial arteries supply the lungs.

While almost any imaginable malformation of heart and great vessels is

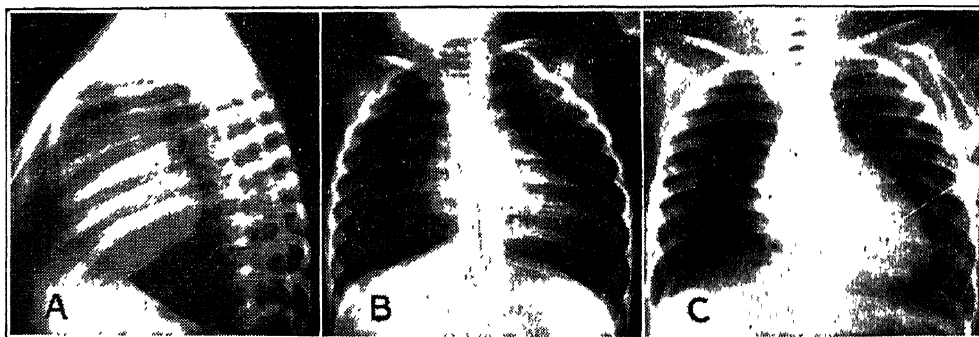


Fig 15—(Case 1) Appearance before and after operation: *A*, Left anterior oblique view before operation; *B*, anteroposterior view before operation; *C*, anteroposterior view after operation. (Blalock, A. and Taussig, H. B : J. A. M. A. 128: 193 (May 19) 1945.)

close to 100 per cent. With ductal ligation, it is reduced to less than 50 per cent. An interesting feature in these cases is the repeated observation that the blood cultures, which are positive for the specific organism before operation, frequently become sterile within a matter of minutes after the ligation.

The specific surgical complications which are liable to occur in this operation are:

- (1) Inability to identify the ductus;
- (2) injury to the duct during a ligation;
- (3) incomplete occlusion or perforation of the ductus by the ligature; and (4)
- injury to the recurrent laryngeal nerve.

possible, those of clinical importance are the ones which permit survival after birth for at least a few weeks, and yet appreciably incapacitate the victims or diminish life expectancy. The incapacitation and diminution in life expectancy are caused by chronic or acute anoxemia, by acute or chronic heart failure or by the superimposition of bacterial infection upon deformed valves or abnormal vascular channels (interventricular septal defects or persistent patent ductus arteriosus).

The recent development of a satisfactory technic of occlusion of a persistent patent ductus arteriosus has presented

us with a satisfactory prophylactic and therapeutic method in the latter conditions where only this defect (persistent patent ductus arteriosus) is present. Anoxemia is not seen in this defect (uncomplicated) since excessive blood enters the pulmonary circulation *via* the ductus. Hence, part of the blood is exposed to oxygenation twice and none is underexposed.

Likewise, in cases of truncus arteriosus where large pulmonary arteries

the supine position. Therefore, in simple septal defects, no anoxemia (or cyanosis) is present.

Cyanosis is only found in cases with high grade anoxemia, being apparent only when at least 5 gm. of hemoglobin (reduced) is present for 100 cc. blood. Lundsgaard and Van Slyke (1923) have shown that there are important factors in the production of cyanosis: (1) The hemoglobin level; (2) the volume of venous blood shunted into the systemic

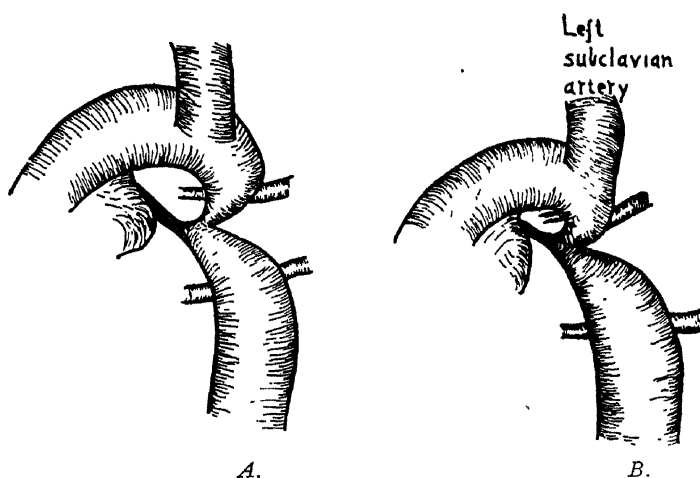


Fig. 16—*A*, Case 1; *B*, case 2. (Crafoord, C. and Nylin, G.: J. Thoracic Surg. 14: 347 (Oct.) 1945.)

arise directly from the aorta, adequate oxygenation of the blood is the rule.

In cases of aortic stenosis or atresia, a similar situation is present. Hence anoxemia (and cyanosis) are rare.

In cases with simple large defect of the intraventricular septum, the flow is usually from left to right because of the higher blood pressure in the systemic circulatory system and in the left ventricle. In cases of interauricular septal defect, the flow again is usually from left to right mainly because of gravity in this case (the left auricle is found above the right in the erect and also in

circulation; (3) the rate of utilization of oxygen by the peripheral tissues, and (4) the extent of aeration of the blood in the lungs. This latter factor depends upon four subfactors: (*a*) Vital capacity of the individual; (*b*) rate of blood flow through the lungs; (*c*) the partial pressure of oxygen in the inspired air, and (*d*) specific pulmonary properties. These latter may include changes such as edema, fibrosis, etc., which interfere with proper absorption of the oxygen from the alveoli. Such changes frequently occur in cases with pronounced polycythemia. Polycythemia is extremely



common in conditions of partial oxygen unsaturation in the arterial blood, probably as part of a compensatory mechanism.

Blalock and Taussig<sup>31</sup> emphasize that with full respect to the importance of these and other factors, persistence of life fundamentally requires the circulation of blood through the lungs. It is

facial shunt of blood from the systemic to the pulmonary circulation comparable to a persistent patent ductus. Such a shunt would be helpful in all cases of congenital heart disease in which there was a deficient pulmonary circulation, commonly cases showing cyanosis.

However, it would be of no value in cases of complete transposition of the

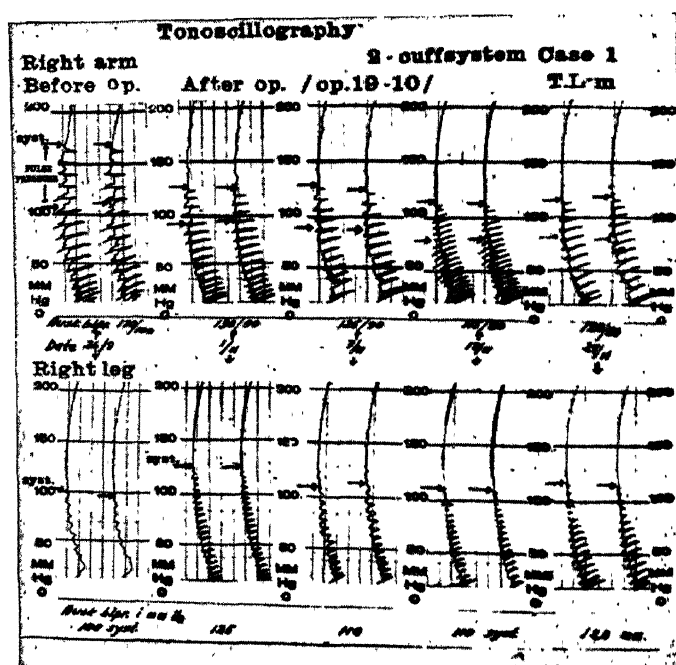


Fig. 17—Tonoscillograms taken before and after operation. (Case 1.) In the arms (the upper curve) there are high blood pressure and good oscillations. In the legs (the lower curve) the pulsations are very small and the blood pressure low.

With the two-cuff system in use here the systolic pressure lies at the point where the oscillations stop (marked by arrows). After operation the systolic pressure decreases in the arms and increases in the legs. (Crafoord, C. and Nylin, G.: *J. Thoracic Surg.* 14: 347 (Oct.) 1945.)

not essential that all the blood pass through the lungs, but there is a minimum requirement for each individual below which life cannot persist. In cases of complete pulmonary atresia, pulmonary circulation may be maintained by a persistent ductus arteriosus. Gradual occlusion of this ductus brings about diminution of this circulation and death.

Therefore, these authors reasoned that such cases could be helped by the arti-

great vessels because the difficulty there is not in the circulation of the pulmonary system but in the inadequate communication between it and the systemic circulation. Unless the pressure in the pulmonary circuit were greater than that in the systemic, the fully oxygenated pulmonary blood could scarcely be distributed throughout the body even if an adequate shunt were produced.

Likewise, in cases of the so-called

"tetralogy of Fallot of the Eisenmenger type," no improvement in the oxygenation of systemic arterial blood could be expected since the important defect here is inadequate absorption of oxygen by the lungs.

Tetralogy of Fallot classically presents: (1) Pulmonary stenosis, and (2) dextroposition of the aorta, with (3) resultant interventricular septal defect,

tion from the involuting ductus. One of the cases presented by Blalock and Tausig was of this type. This condition is similar to that of truncus arteriosus with the pulmonary arteries arising congenitally from the bronchial arterial supply.

Therefore, such an operation should benefit cases of tetralogy of Fallot, pulmonary atresia, truncus arteriosus with bronchial arteries, and cases with a sin-

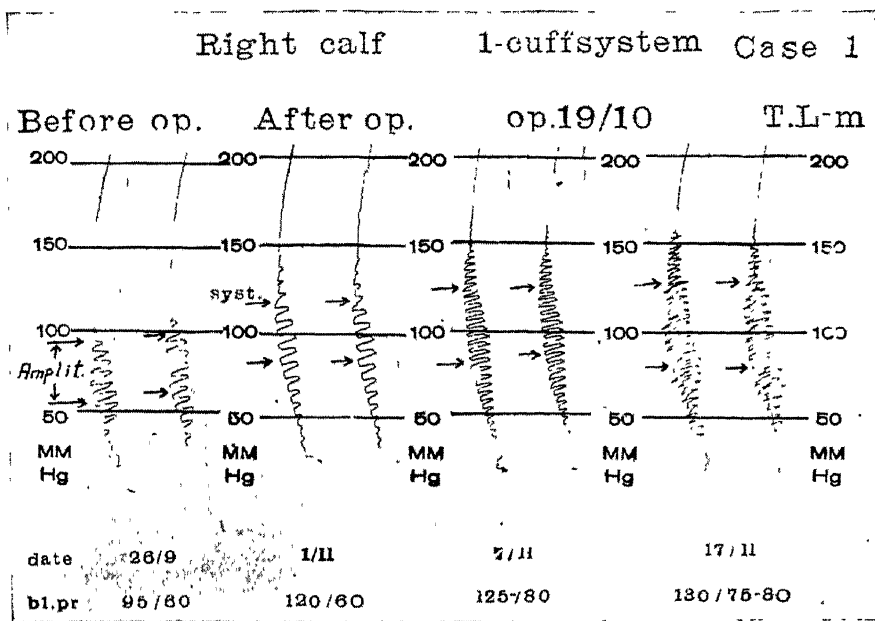


Fig. 18—Tonoscillograms from the right calf of the patient (case 1), before and after operation; one-cuff system. Both the systolic and the diastolic blood pressure increase after operation (marked by arrows). (Crafoord, C. and Nylin, G.: *J. Thoracic Surg.* 14: 347 (Oct.) 1945.)

and (4) resultant right ventricular hypertrophy. This is the commonest combination of congenital cardiac defects attended by cyanosis.

In cases of similar defect with complete atresia of the pulmonary artery, a widely persistent patent ductus arteriosus is always present. The only exception to this is the rare individual who has developed sufficient collateral enlargement of bronchial and small hilar vessels to replace the gradually diminishing circula-

tion from the involuting ductus. One of the cases presented by Blalock and Tausig was of this type. This condition is similar to that of truncus arteriosus with the pulmonary arteries arising congenitally from the bronchial arterial supply.

**Technic of Operation:** Depending upon the assumed amount of additional blood needed for an adequate pulmonary circulation, either the innominate or left subclavian artery is chosen for the procedure. Since most cases referred for treatment are in a serious state of underoxygenation, the larger innominate artery is usually preferable. The incision is made through the third anterior intercostal space. The appropriate pulmonary artery is exposed practically from its origin to its first branches.

On the right side it is necessary to divide the communicating branch of the azygos vein and to retract the superior vena cava medially.

The innominate artery is exposed to its bifurcation or the left subclavian beyond the origin of the thyrocervical trunk. The distal branches are ligated (proximal of the thyrocervical trunk, too) and the vessel is cut after applying a bulldog clamp across it, close to its origin from the aorta. Two more such clamps are applied across the pulmonary artery at either extremity of exposure. A transverse

largement has been the rule (see Fig. 15). In spite of this, no evidence of congestive heart failure has yet been manifested. Naturally, there is no long-term follow-up, the first case having been operated November 29, 1944. And, of course, no prediction as to the possibility of superimposition of bacterial infection upon the congenital or artificially produced abnormalities can be offered.



Fig. 19—Distortion of esophagus caused by intramural fibroma. (Adams, R. and Hoover, W. B.: *J. Thoracic Surg.* 14: 279 (Aug.) 1945.)

incision is made in the presenting wall of the pulmonary artery and an anastomosis is made between the end of the systemic artery and the side of the pulmonary artery (Figs. 13 and 14). Fine arterial silk on a curved needle is used. The clamps are then removed, the one on the systemic vessel last. Any bleeding point is controlled by an extra suture or two.

The patients stand the procedure well, and results have so far been gratifying both clinically and from the laboratory standpoint. There is additional strain thrown upon the left ventricle by this procedure, and postoperative cardiac en-

It does not seem, however, that the possibilities of such eventualities should deter us from preventing immediately impending death from anoxemia.

Blalock and Taussig have discussed other (four) operative procedures which might offer somewhat similar results. One and two of these are the anastomosis of subclavian or innominate artery respectively to the pulmonary end of a divided main or an upper lobe pulmonary artery. Such a procedure might well be invoked if during the course of

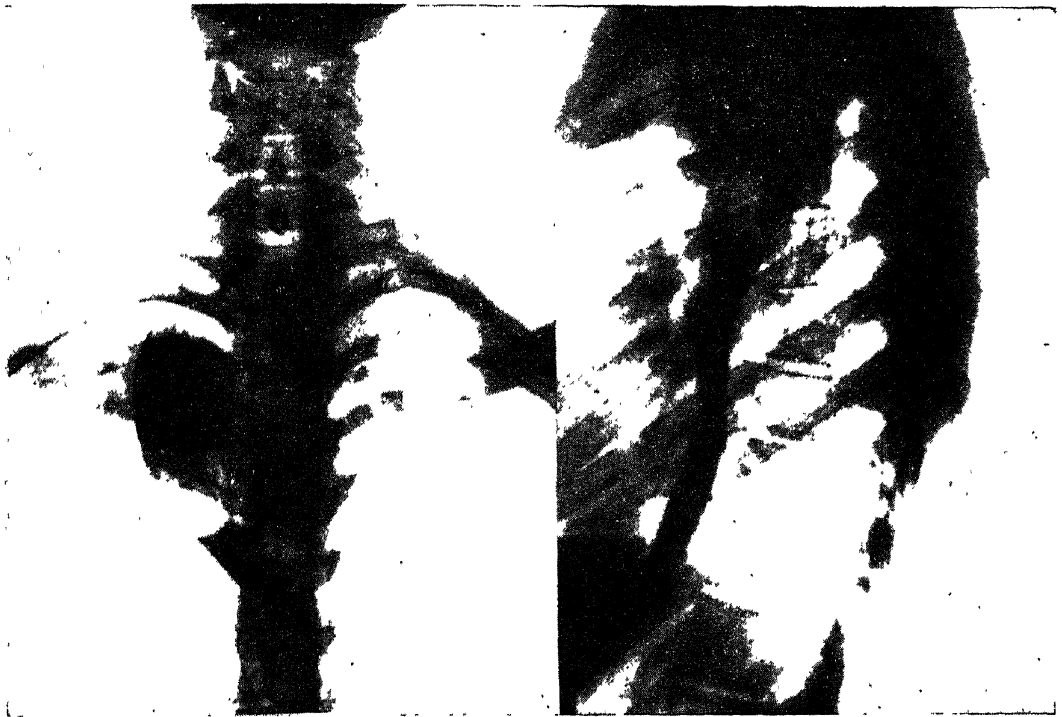
the end-to-side anastomosis of peripheral vessel to pulmonary the latter should become irreparably injured. The procedure could then be readily changed to one of these after ligating the proximal end of the pulmonary artery.

Procedure three would be the anastomosis of the side of the descending arch of the aorta to the left pulmonary artery. Leeds (1943) has already performed such anastomoses in animals.

may prove to be the ideal one in a newborn infant with severe pulmonary atresia or stenosis.

Anticoagulant drugs were not used until the third or fourth day. Enough *dicumarol* was then employed to keep the clotting time at approximately double normal values.

In the two patients in which arterial oxygen studies were performed, the oxygen saturation rose from 36.3 per cent



Figs. 20 and 21—Esophageal changes associated with pedunculated intraluminal fibroma. (Adams, R. and Hoover, W. B.: J. Thoracic Surg. 14: 279 (Aug.) 1945.)

However, in some cases, paralysis of the legs of the animals resulted from prolonged interruption of the circulation in the descending aorta. Therefore, this procedure was not considered favorably.

Procedure four is the anastomosis of the aorta to the main pulmonary artery. This can be performed in a few seconds by a stab wound made by introducing a knife through the opposite free wall of the pulmonary artery which can then be closed by a few sutures. This procedure

and 35.5 per cent respectively to 82.8 per cent and 83.8 per cent within four weeks after operation. There was likewise diminution in the polycythemia and high hemoglobin levels to more nearly normal levels. The clinical improvement was dramatic.

The authors stress that such an operation should not be performed unless both clinical (cyanosis) and radiologic (no pulsations at hili of lungs and no prominent pulmonary conus) evidences of

decreased pulmonary blood flow are present.

**Congenital Coarctation of the Aorta**—Congenital coarctation of the aorta is a condition in which there is a severe constriction or stenosis of the aorta just distal to the origin of the left subclavian artery. It is characterized by normal or hypertensive blood pressure (usually the latter) in the upper ex-

by diodrast reveals the typical deformity (Fig. 16).

Crafoord and Nylin<sup>32</sup> report two operative cases. The aorta is clamped just beyond the area of stenosis with bulldog arterial clamps. All collaterals are similarly occluded. The stenotic area is then resected, being careful to produce equal-sized openings in the vessel ends. These ends are then anastomosed by the Carrel

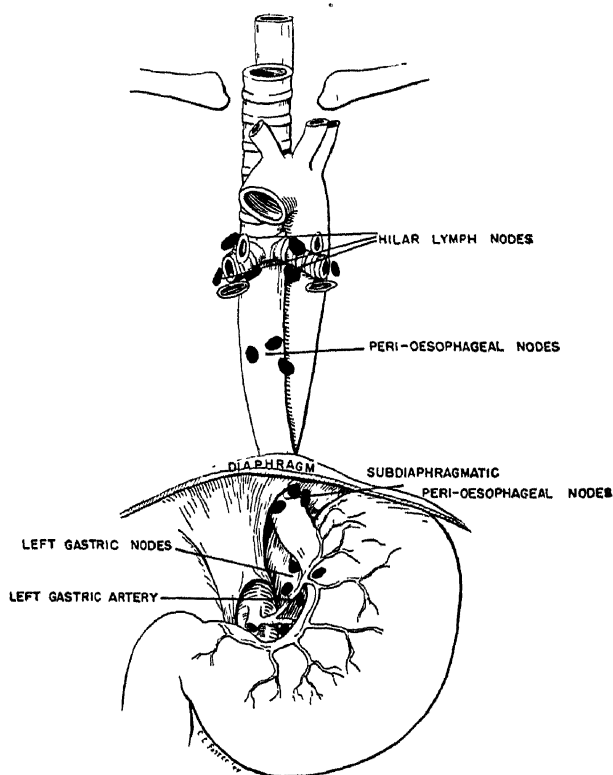


Fig. 22—The most frequent sites of lymph-node invasion in cases of carcinoma of the esophagus. (Sweet, R. H : Clinics 3 : 1288 (Feb.) 1945.)

tremities, and lower or imperceptible blood pressure in the lower extremities. There is frequently extensive development of arterial collaterals, particularly of the internal mammary and intercostal vessels. Enlargement and tortuosity of these latter vessels are responsible for characteristic erosions or notchings of the under surfaces of the ribs. This is demonstrable by roentgenograms. Radiography after opacification of the aorta

method. The clamps are released and the circulation to the lower part of the body is restored. In one case the circulation was thus diverted for twenty-seven minutes without untoward effect. Five months after operation in both cases the blood pressure in the arms had dropped from hypertensive levels to nearly normal, and that in the legs had risen to somewhat higher levels than in the arms.

Gross<sup>30</sup> feels that aortic coarctation is a condition of variable degree and thus varies in producing incapacity of negligible amount or extreme shortening of life expectancy. Aneurysmal dilatation, rupture of the aorta, or superimposed *Streptococcus viridans* infection sometimes occur. Hypertension and its sequelae of cardiac strain and cerebral complications are the more ordinary results.

After a prolonged period of animal experimentation, a practical method of

No pulsations or blood pressure determinations could be obtained in the legs. Posterolateral incision was made. Several intercostal arteries were doubly ligated and divided. The aorta was then clamped and the constricted portion excised. (There was no lumen through it.) Continuous mattress suture with eversion of the aortic edges was applied (00000 Deknatel silk No. X atraumatic needle, 0.5 mm. and 9 mm. long). Anastomosis took twenty-three minutes.

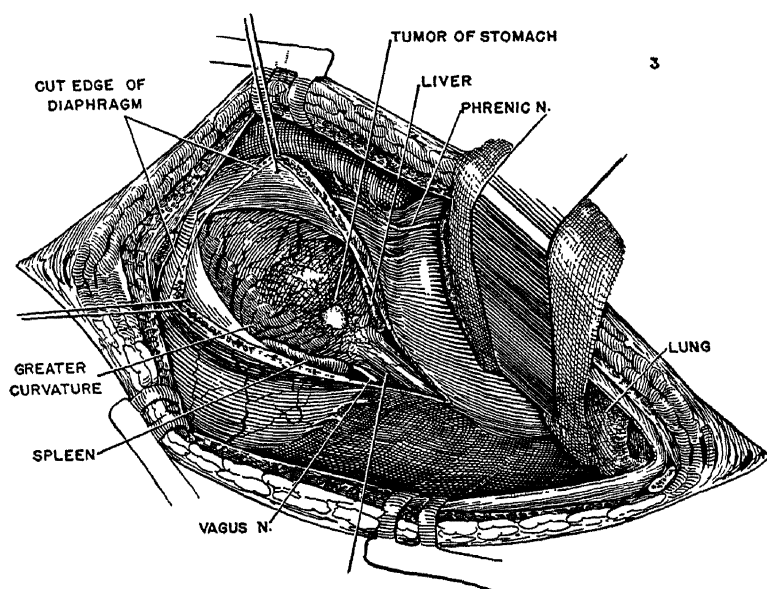


Fig. 23—Transthoracic approach to the stomach—anatomy of the field of operation after incision of the diaphragm. (Sweet, R. H.: Clinics 3: 1288 (Feb.) 1945.)

resection of the stenosed aortic segment and end-to-end anastomosis has been worked out.

The first patient was a five-year-old boy with hypertension in the arms and deficient circulation in the legs. After the anastomosis, the clamps were quickly removed resulting in loss of blood pressure because of opening of the huge vascular bed, and death soon followed.

The second case was a twelve-year-old girl with blood pressure in the arms of 160 to 220 systolic and 98 to 152 diastolic. She had severe headaches, changes in the retinal vessels, and papilledema.

1. The proximal clamp was released over a period of ten minutes.

2. The patient was kept in Trendelenberg position to diminish pooling in the legs and abdomen.

3. Donor blood was pumped rapidly into the ankle cannula to augment venous return.

*Penicillin* was used, 120,000 units daily intramuscularly for four days. No heparin or dicumarol was used.

At discharge after nineteen days, blood pressure in arm was 140/80. In the legs, blood pressure was 145/105. (See Figs. 17 and 18.)

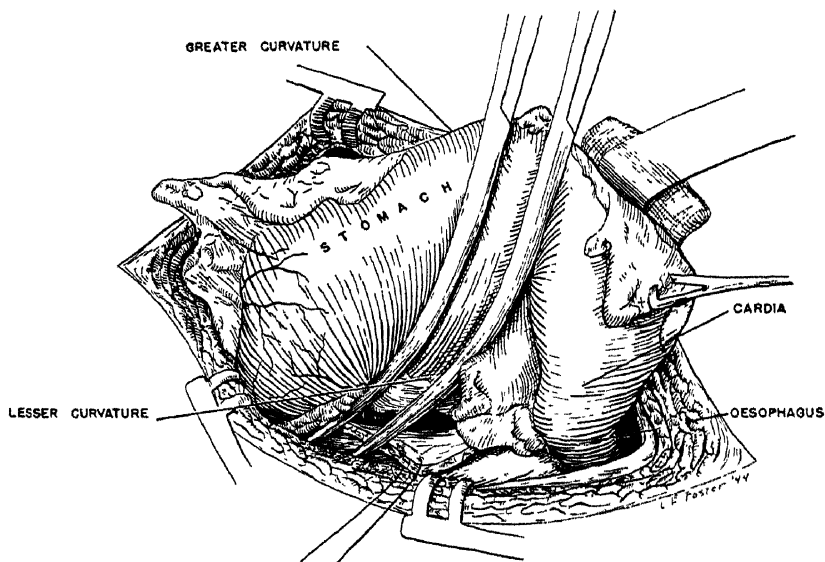


Fig. 24—Partial gastrectomy for carcinoma near the cardia of the stomach. Upper half of the stomach has been mobilized. The greater curvature is turned upward. Large curved clamps have been placed across at the optimum point. The stomach is to be divided by cutting close to the distal clamp. (Sweet, R. H.: Clinics 3:1288 (Feb.) 1945.)

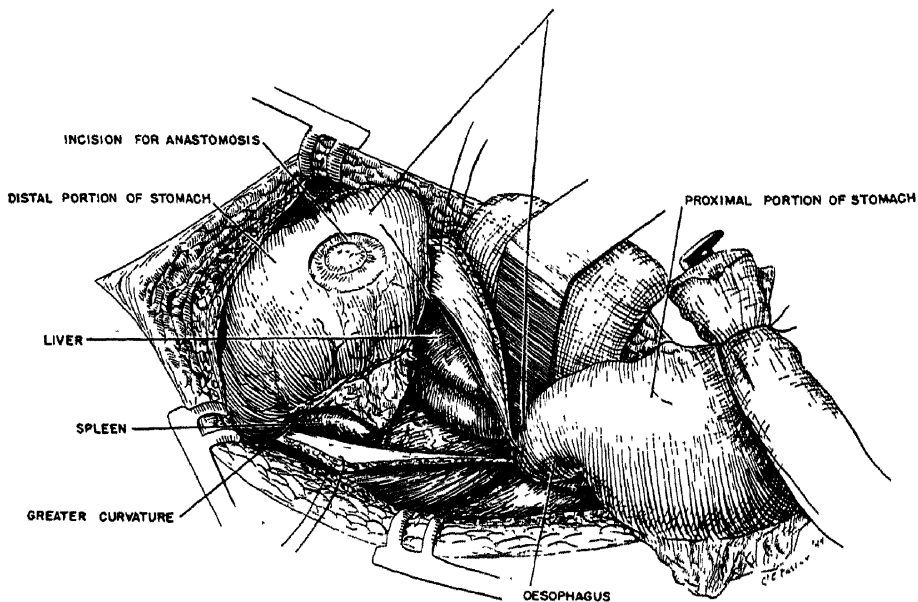


Fig. 25—Partial gastrectomy for carcinoma near the cardia of the stomach. Division of the stomach has been completed. The cut edge of the distal portion has been inverted. A circular incision in the anterior wall of the distal portion has been made and the first suture between the stomach and the esophagus on the outer layer of the posterior portion is shown started. (Sweet, R. H.: Clinics 3:1288 (Feb.) 1945.)

### Benign Tumors of the Esophagus

Adams and Hoover<sup>33</sup> report three cases of benign tumor of the esophagus. These are extremely rare tumors which present peculiar and difficult problems of diagnosis and treatment.

They may be submucosal (perhaps pedunculated), intramural, or extramural.

is much less marked and later in occurrence than in carcinoma of the esophagus.

X-ray after swallowing barium reveals the outline of the mass when it is submucosal or polypoid.

The first case was an essentially intramural fibroma (Fig. 19) in the cervical esophagus. It was removed through a

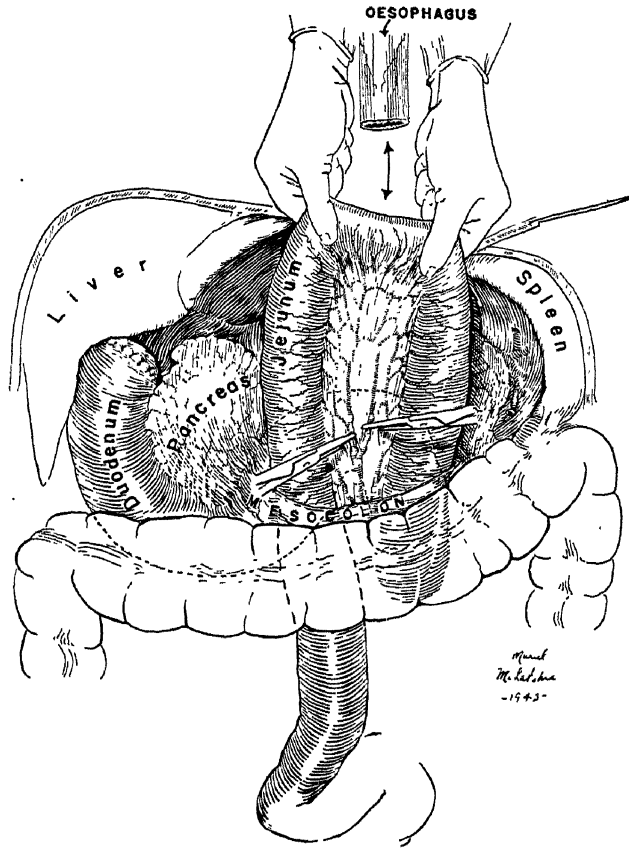


Fig. 26—Total gastrectomy. Proximal loop of jejunum drawn up through transverse mesocolon. The pull of the mesenteric vessels makes it impossible to extend the apex of the loop much above the level of the diaphragm. Anastomosis with the esophagus not possible without release of the pull of the mesenteric vessels. Point of division of these vessels shown by hemostatic forceps in the drawings. (Sweet, R. H.: *Clinics* 3:1288 (Feb.) 1945.)

They may be leiomyomas, myomas, fibromas, myxomas, hemangiomas, papillomas, polyps, etc. They may occur in any portion of the esophagus.

Symptoms vary from none to cough, dyspnea, cyanosis, dysphagia, substernal pain, etc. Occasionally the mass may be regurgitated into the mouth. Dysphagia

cervical esophagotomy without opening the mucosa of the esophagus. The second case (see Figs. 20 and 21) was a pedunculated fibroma removed by trans-thoracic esophagotomy, traversing and repairing the mucosa of the esophagus. The third case was a polyp arising from the region of the cricopharyngeus muscle



which was removable by the peroral endoscopic snare. This last method must be considered ideal where feasible since it avoids the risk of open operation with its attendant dangers of leakage and mediastinitis.

operation, a mortality of 40 per cent which is well within the usual limits for these procedures.

The authors stress that these operations are indicated even as a palliative when there is justifiable belief that life

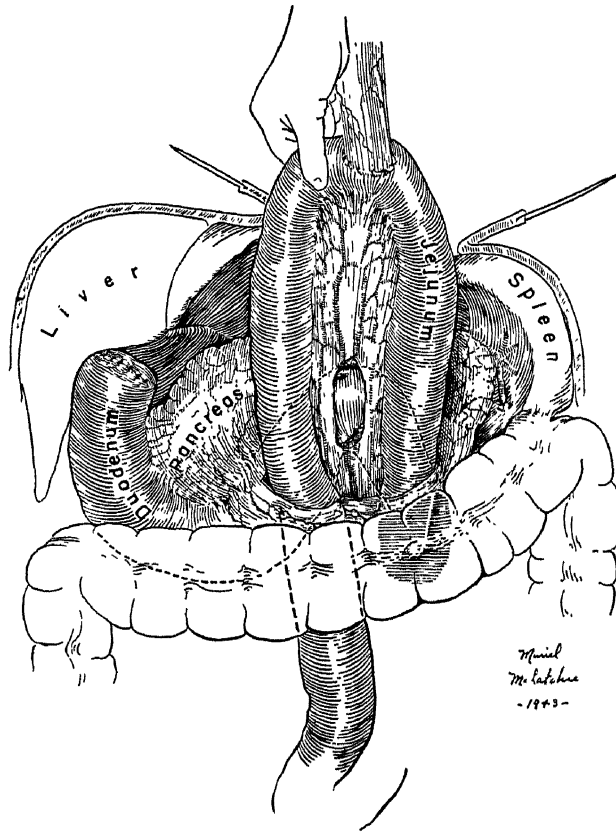


Fig. 27—Total gastrectomy. Marked release of tension after division of mesenteric vessels makes it possible to bring the proximal loop of jejunum high above the diaphragm into the chest, and the esophagojejunostomy is performed without tension on its suture line. (Sweet, R. H.: Clinics 3:1288 (Feb.) 1945.)

### Lower Esophagus and Upper Stomach Lesions

Bradshaw and O'Neill<sup>4</sup> report five cases, two total gastrectomies with esophagojejunal anastomosis, and three subtotal gastrectomies, one with esophagojejunal and two with esophagogastric anastomosis. One of the total gastrectomies was for ulcer. There was no evidence of leakage from the anastomosis in any case. Two deaths occurred from

may be prolonged or made more pleasant by providing a means of ingestion of food. The distress associated with starvation or life with a permanent gastrostomy certainly does not add up to the comfort associated with successful local resection and anastomosis even though recurrence may be certain.

Sweet<sup>34</sup> reports upon eighty-three patients in whom radical transthoracic resection of the esophagus or stomach

has been performed for carcinoma. This series includes fourteen cases in which the Torek procedure (local resection of the esophageal lesion with exteriorization of the upper segment usually following a permanent gastrostomy) was used. The total operative mortality was 12 per cent in resections of the lower esophagus, cardia, and fundus.

esophagogastric resection and immediate anastomosis.

The wide exposure afforded by the transthoracic approach of both upper abdomen and mediastinum not only permits total gastrectomy and esophagojejunal anastomosis, but also renders feasible the resection of high (supra-aortic) esophageal neoplasms and dis-

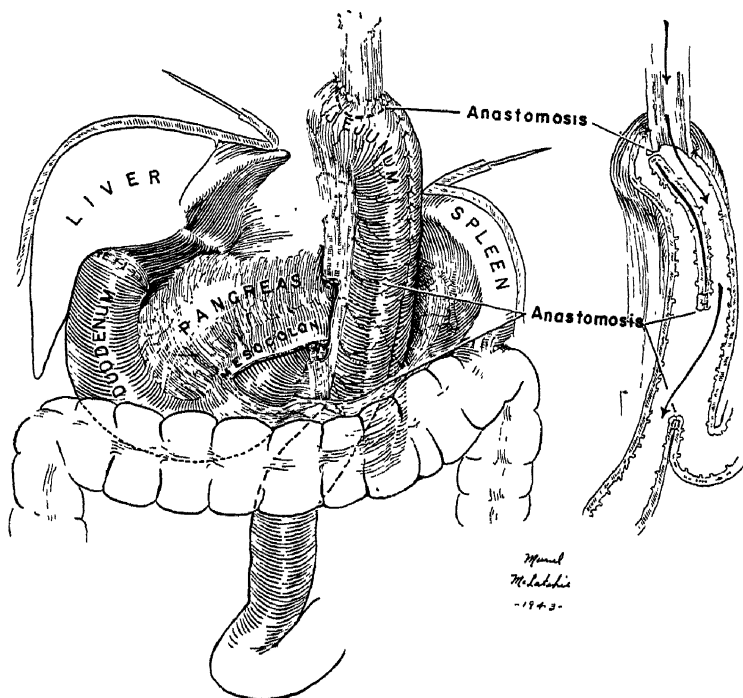


Fig. 28—Total gastrectomy. Completed anastomosis. Roscoe Graham technic used to reinforce the line of suture. Enteroenterostomy between the afferent and efferent arms of the jejunal loop shown just above the level of the opening in the transverse mesocolon. Insert shows vertical section of lower esophagus and jejunal loop to which it has been anastomosed—enteroenterostomy shown. (Sweet, R. H.: Clinics 3:1288 (Feb.) 1945.)

He feels that the Torek procedure is now outmoded since it does not permit proper extirpation of some of the regional draining lymph nodes (those about the abdominal esophagus and the left gastric artery), it leaves the patient with unesthetic and unphysiologic exteriorization of his upper alimentary canal (the continuity of which can only be reestablished by multiple time-consuming plastic procedures), and because even the original operative mortality of this procedure is no lower than that of

placement of the entire stomach into the thorax for easy esophagogastric anastomosis.

Carcinoma of the true esophagus is a squamous cell type, but adenocarcinoma may arise from the stomach and extend up the esophagus, or from either a tongue of gastric mucosa extending upward from the cardia, or from an island of aberrant gastric mucosa in the esophagus. Leiomyomata and leiomyosarcomata arise occasionally in the stomach. The common gastric carcinoma is an

adenocarcinoma. Carcinoma of the esophagus often extends through the submucosal layers beyond the apparent limits of the growth. Therefore an adequate margin must be included in the resection.

**Metastasis**—Lymph node metastasis in true esophageal lesions is usually seen

periesophageal area, those about the left gastric vessels, and those in the gastrolienal and gastrocolic ligaments. Later the retroperitoneal periaortic nodes, and those near the antrum of stomach and first portion of the duodenum are involved. Esophageal carcinoma seldom



Fig. 29—Specimen removed in a case of carcinoma of the midthoracic esophagus, extending almost to the aortic arch. The specimen has been opened to show the interior of the esophagus and a rim of cardiac portion of the stomach. Near the bottom are three large masses of lymph nodes. (Sweet, R. H. . Clinics 3: 1288 (Feb.) 1945.)

in four areas: (1) Nodes about the pulmonary hili; (2) a ring of periesophageal nodes near the inferior pulmonary vein; (3) a ring of nodes around the abdominal esophagus, and (4) nodes about the left gastric artery.

Gastric carcinomas tend to metastasize to nodes in the supradiaphragmatic

produces pleural carcinomatosis and effusion, and rarely involves the liver. Carcinoma of the stomach may involve the liver early and frequently produces peritoneal carcinomatosis or pelvic implants.

The tendency of high esophageal lesions to directly invade adjacent structures, such as the aorta, left main bron-

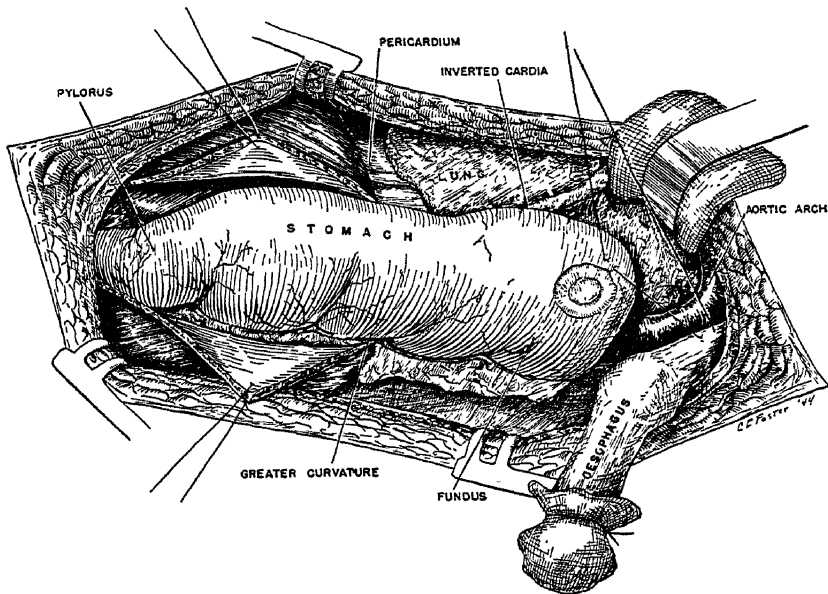


Fig. 30—High esophagogastric anastomosis for carcinoma of the midthoracic esophagus. The esophagus has been completely mobilized and pulled out from behind the aortic arch. The stomach, after complete mobilization preserving the right gastric and right gastroepiploic vessels, is shown pulled high into the chest so as to make possible an anastomosis at or just above the level of the aortic arch. (Sweet, R. H.: Clinics 3: 1288 (Feb.) 1945.)

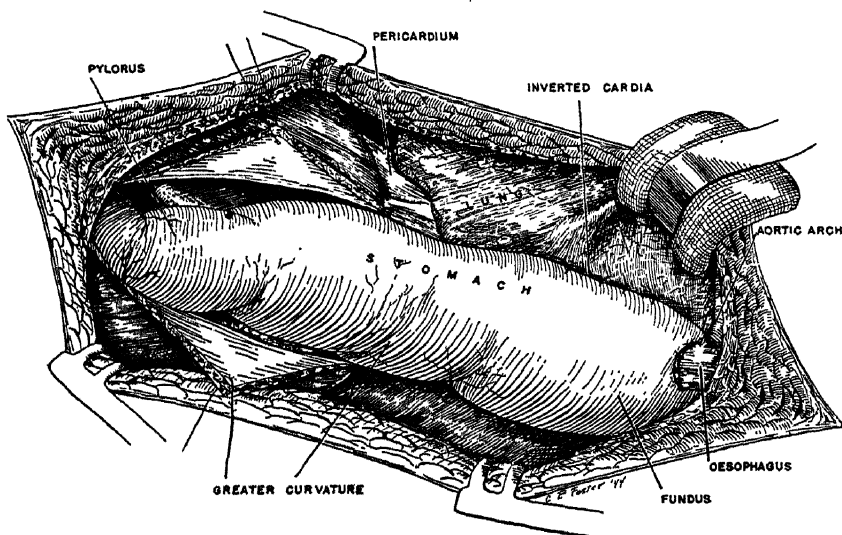


Fig. 31—High anteaortic esophagogastric anastomosis completed. (Sweet, R. H.: Clinics 3: 1288 (Feb.) 1945.)

chus, the inferior pulmonary vein, and the left pulmonary artery, the left recurrent laryngeal nerve, and mediastinal pleura is responsible for the low resectability of tumors in this region. Lower lesions tend to involve the mediastinal pleura which must then be resected, but present an operability level of 80 per cent. Gastric carcinomas may directly invade the adjacent liver (left lobe), pancreas, spleen, adrenal gland, and diaphragm. Portions of these organs may be resected along with the growth. (Figs. 22, 23, 24, 25, 26, 27, 28, 29, 30, 31.)

The essentials of Sweet's operation of partial gastrectomy and esophagectomy with esophagogastric anastomosis are as follows:

1. The diaphragm is incised from the costal margin to the hiatus.
2. The lower three to four inches of esophagus are mobilized along with periesophageal nodes, and the vagus nerves are divided.
3. The upper end of the stomach is mobilized by dividing the structures behind the cardia, and the spleen is freed by cutting the gastrosplenic ligament and vasa brevia.
4. The left gastric vessels are divided far away from the stomach.
5. The gastrocolic ligament is divided down to the antrum of the stomach. The gastroepiploic arteries are divided here.
6. Two curved crushing clamps are put on the stomach so as to leave as much of the greater curvature as possible and the stomach is cut between the clamps.
7. The tumor is covered by a rubber glove and the distal cut end of the stomach is closed.
8. A circular opening is made in the anterior gastric wall and an end-to-side esophagogastric anastomosis is performed.
9. The diaphragm is sutured to the stomach wall after being paralyzed by crushing the exposed phrenic nerve.

The bilateral vagotomy reduces appetite, gastric peristalsis, and vomiting. It increases pyloric tone (even to the point of spasm).

The presence of a large portion of the stomach in the chest causes few or no symptoms.

### Visceral Strangulation Complicating Delivery in Cases of Diaphragmatic Hernia

A thirty-one-year-old white female in her second pregnancy had a history of normal labor the first time. The delivery was also normal the second time. Five hours later severe epigastric distress, vomiting, dyspnea, cyanosis occurred.

Immediate operation was performed through the abdominal approach. Reduction of hernia was performed, all the hollow viscera being found in the chest. Uneventful recovery.

Medical literature reveals four fatal cases of diaphragmatic hernia in pregnancy. One was diagnosed premortem. Two became ill and died on the day of delivery.

Two other reported cases of diaphragmatic hernia complicating the puerperium were treated conservatively, successfully.

**Summary** — Certainly many women with diaphragmatic hernia come to pregnancy each year. They should be diagnosed early in the course of pregnancy. In the early months they should be subjected to elective surgery.

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## WAR INJURIES OF THE CHEST

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The mortality as well as the morbidity of wounds of the chest has always been considerable. By application of recent advances in chest surgery and an appreciation of the importance of rapid re-establishment and maintenance of normal respiratory physiology, combined more recently with the beneficial effects of special chemotherapeutic agents, as the sulfonamides and penicillin, both the morbidity and the mortality have been greatly reduced.

The purpose of this chapter is to present the types of cases encountered, their management, and observations made either in the course or treatment of the injuries.

### Preoperative Management

It was early learned during the recent war that preoperative preparation of

chest cases in a forward hospital installation during active combat could be adequately carried out only if the service was so organized that all cases, regardless of severity, were admitted to a fixed ward, namely, the shock ward. On admission to the shock wards, all patients received *oxygen* through a BLB mask, and *plasma* therapy was instituted. Detailed examination of the patient was then carried out with emphasis being placed on the examination of the wound, as it was not uncommon to find patients with "sucking wounds" of the chest who either, because of inadequate dressing or derangement of adequate dressing in transit, arrived at the hospital with their wounds still sucking. Adequate dressing closure was accomplished by the use of large strips of vaseline gauze and a firmly applied

gauze pad. Packing was not practiced and is strongly condemned. Physical examination of the chest is done in all cases. *Morphine* is used where indicated but never in doses greater than 15 mg. ( $\frac{1}{4}$  grain). Codeine is never used. All patients are made to lie on the affected side in a semirecumbent position. Shock was combatted by the use of large quantities (1000 to 3000 cc.) of plasma and whole blood. It must be emphasized that in patients with serious chest wounds whole blood transfusions are imperative. Plasma *per se* is inadequate in stabilizing patients who have had serious blood loss. Quantities of whole blood up to 2500 cc. are often administered with gratifying results. No patient in shock, unless actively bleeding, is ever operated until he is well stabilized.

On several occasions a valvular tension pneumothorax may have to be decompressed on the spot because of the patient's critical condition.

All patients with few exceptions should have an *A-P* and *lateral film* of the chest, *fluoroscopy*, and a flat plate of the abdomen taken prior to surgery.

### Anesthesia

In operations upon the thorax, the anesthetist assumes a rôle of great responsibility for he must frequently work with poor risk patients. His skill and management are primary factors in the successful outcome of many thoracic surgical procedures for which he too often is not given sufficient recognition.

Anesthesia used in chest trauma should be one of two forms. Endotracheal closed anesthesia, using *cyclopropane*, *ether*, or *nitrous oxide* (*ether* with positive pressure or controlled respiration technic should be used in all open cases which includes exploratory thoracotomy and the débridement and closure of open pneumothoraces).

*Local anesthesia* and *intercostal nerve block* should be employed for all procedures involving only the chest wall and for thoracentesis. It is strongly felt that all forms of intravenous anesthesia are contraindicated in early war injuries of the chest.

Aspiration of the tracheobronchial tree should be done on all patients that received general anesthesia at the completion of the operation.

### Penetrating Wounds

**Hemothorax** — This condition, in which visible accumulation of blood in the pleural cavity is the most important abnormality, is the most commonly met lesion in chest trauma. Many of these cases reveal the presence of retained metallic foreign bodies of small size (less than 1 x 2 cm.), which, from the standpoint of effect on early management, are considered nonexistent.

These patients present the typical signs, symptoms, and x-ray findings of pleural effusion and the blood present in the pleural cavity may vary from small accumulations in the sulci, with little or no reduction in vital capacity, to massive accumulations with marked diminution in vital capacity and the classical signs of oxygen want.

The etiology of the hemothorax is in most cases: (1) Bleeding from the chest wall, and/or (2) lung bleeding.

Hilar structures, when involved, usually cause rapid death, or, if the patients arrive at a hospital installation, they are such in *extremis* that surgery is not advisable.

Intercostal artery hemorrhage is a common etiological factor in hemothorax; as a result of stab wounds of the chest, it is a common finding in civilian practice. Surprisingly, at no time was intercostal artery ligation for hemorrhage necessary in a personal series of

over 700 war injuries of the chest. In many cases, during débridement or exploration, the vessels were visualized and found to be torn, but well thrombosed.

Lung bleeding undoubtedly occurs in all cases of hemothorax, but is usually self-controlled and rarely recurs. However, a number of cases with extensively lacerated lobes do not control themselves and lung suture is necessary to control hemorrhage.

The management of patients with hemothorax is undoubtedly one of the most important considerations of the thoracic surgeon, especially in front line hospitals. The greatest error made in the treatment of these cases is that of ultraconservatism, the tendency to leave the patient alone because he is apparently doing very well. Added to this is the utter confusion on this subject that appears in the literature, early outdated teaching, and inexperience.

There are three considerations in the management of these cases:

1. The patient.
2. The wound.
3. The hemothorax.

1. **The Patient**—Often during the stress of battle, when a hospital is filled to overflowing with battle casualties, the patient as an individual is forgotten. He becomes a "compound femur," a "belly," or a "chest." Patients with chest wounds are often apprehensive, and a very important phase of the treatment is the reassurance that all will go well. In terms understood by a layman, the hemoptysis and dyspnea are explained and their importance minimized, and the question that must always be answered is, will they be able to resume normal lives when they are well. These patients seem to have an inborn knowledge of what it means to be a respiratory cripple.

2. **The Wound**—When patients were well stabilized, and only then is attention

directed at the wound. All wounds of entrance, unless grossly infected or very small and clean, regardless of hours after injury are débrided, and loosely packed with *vaseline gauze*. The local use of sulfanilamide powder is no longer practiced. Local anesthesia is used in most débridements.

3. **The Hemothorax**—The management of the hemothorax has been a subject of considerable controversy in the present-day literature. Numerous writers, some with very small series of cases, have advocated varied methods of treatment, many of which do not take into account the basic fundamentals of respiratory physiology and the mechanics of pleural space infection.

In the treatment of hemothorax, the surgeon is confronted with three basic considerations:

- (a) Progression of the hemothorax.
- (b) Early reexpansion of the lung.
- (c) Pleural space infection.

(a) **PROGRESSION OF THE HEMOTHORAX**—This is an ever-present possibility in all war injuries of the chest, and, therefore, becomes the first problem to be dealt with by the thoracic surgeon. The lack of response to adequate shock therapy, or a transient response with rapid return to the shock state, and increasing dyspnea, are indications that active bleeding is present. When bleeding is suspected, thoracentesis is done immediately, and as much blood removed as can be aspirated. Thoracentesis is repeated in an hour, and if a large quantity of blood is removed at this second aspiration, one is reasonably sure that active bleeding is present and exploration of the chest wall or lung, or both, is indicated.

Autotransfusion may be practiced following diagnostic thoracentesis. However, it is not very strongly recommended if the time of injury exceeds



twelve hours as gross infection in a hemothorax may occur very early.

(b) **EARLY REEXPANSION OF THE LUNG**—The active management of all patients with hemothorax is concerned primarily with directing treatment toward early reexpansion of the lung. There is one and only one method of treatment which will favor early reexpansion of the lung; namely, early and repeated *aspiration* without air replacement. Points of considerable controversy in the present-day literature are: (1) When to institute thoracentesis? (2) How much blood should be removed at each aspiration? (3) When should aspirations be repeated? (4) Should air replacement be instituted?

Thoracentesis is usually instituted twenty-four hours after wounding, although there should be no hesitation felt about aspirating hemothoraces earlier in many cases. Aspiration is usually done twenty-four hours after injury because it is believed that patients are better stabilized both systemically and locally at this time. It must be emphasized that there is little or no danger of recurrence of bleeding (lung bleeding) as the result of early aspiration. In no case in a large personal series did bleeding recur following aspiration twenty-four hours after injury or in the cases where it was instituted earlier.

How much blood should be removed at each aspiration has been a subject of considerable discussion. Early in the war, quantities of blood varying between 400 to 600 cc. were removed at each aspiration if obtainable, never more. As experience was gained in the treatment of hemothorax, no limit was placed on the amount of blood removed at each aspiration. All patients are now aspirated as dry as possible, with quantities as high as 2200 cc. having been

removed at a single aspiration. This procedure is very well tolerated by most patients, the number of aspirations necessary is very definitely reduced, early reexpansion is favored, and the incidence of clotting in the hemothorax is undoubtedly reduced. The most common untoward effect noted in most patients is referred pain to the shoulder of the affected side, which usually subsides after several hours without sedation. A very small number of patients may complain of tightness in the chest, which also subsides after several hours without specific treatment.

Aspirations are repeated daily, with no limit placed on the quantity of blood removed at each aspiration.

The question of air replacement will probably be argued for a long time to come. It is mentioned here only to condemn its use in the treatment of hemothorax. All are agreed that the purpose of air replacement is to prevent the recurrence of bleeding from lung laceration. It is of no value in controlling bleeding from the chest wall. The experience of many surgeons who have treated relatively large numbers of cases has been that recurrence of bleeding rarely occurs. If the experience of most men who have managed a considerable number of these cases has been that recurrence of bleeding rarely if ever occurs, then one must ask the question, "Why air replacement?" Why institute a form of therapy for which there are no indications? Most important is the fact that air replacement has a very definite disadvantage, namely, the resulting pneumothorax will temporarily prevent the apex of the lung from reexpanding or collapse an already expanded apex. This is particularly dangerous because if a pleural space infection occurs, and a very definite percentage of

patients with war wounds of the chest will develop pleural space infections, a total empyema with its resultant high morbidity and mortality rate will result.

(c) **PLEURAL SPACE INFECTION**—In patients with war wounds of the chest, there will undoubtedly always be an incidence of pleural space infection regardless of the care and diligence expended in the management of these cases. However, this incidence will be markedly reduced, and, in those cases in which infection results, the space will be a small one, if one institutes (1) early and repeated aspiration; (2) no air replacement; (3) removal of large metallic foreign bodies or nonmetallic elements, such as clothing and rib fragments; (4) chemotherapy; (5) *penicillin* therapy, both parenterally and locally.

Supportive treatment of patients with hemothorax included the routine administration of *sulfadiazine* in dosages of 8 gm. the first day followed by 6 gm. daily for the next four days. *Penicillin* was administered in dosages of 20,000 units every three hours, and instillations of 50,000 to 100,000 units of penicillin into the pleural cavity were routine after each thoracentesis. *Oxygen* was administered by a BLB mask to all patients who exhibited dyspnea, with or without cyanosis. Parenteral fluids were administered whenever necessary to maintain normal fluid balance, plasma being used freely to maintain normal blood protein levels. All patients received a *high protein full diet* supplemented by large doses of *vitamin C*. *Cough* and *expectoration* were mandatory, and, in patients with multiple rib fractures, this process was aided by the use of intercostal nerve block. Bronchoscopy should be used for patients who refuse to cough. *Deep breathing exercises* every hour are routine. Cough depressants (codeine, etc.) are contraindicated.

**Infected Hemothorax**—This complication is usually not seen until the second week after injury, although several incidences are reported of grossly infected hemothoraces occurring readily within twenty-four hours of injury. This diagnosis is usually made from a septic temperature, leukocytosis and the removal of foul-smelling blood from the pleural cavity. Culture of the fluid usually reveals mixed organisms.

Management of these cases consists of daily *thoracentesis* with instillation of 50,000 to 100,000 units of *penicillin*—establishment of closed drainage until localization occurs, followed by open thoracotomy.

**Closed Pneumothorax**—The incidence of closed pneumothorax, the result of penetrating wounds of the chest, is relatively low. It has been noted that in a majority of these cases wounds were in the upper anterior portion of the chest, the incidence being divided between the supra- and infraclavicular regions. In most cases, wounds of entrance are small. Physical signs usually depend on the extent of the pneumothorax present. In small pneumothoraces, there may be very few physical signs, whereas in the larger pneumothoraces classical signs are readily elicited.

Management of these cases consists of *wound excision*, *bed rest*, and decompression of the pneumothorax by *closed drainage*. With small accumulations of air, bed rest is usually sufficient and absorption of the air occurs without specific treatment.

**Open Pneumothorax (Sucking Wounds)**—This group of patients probably represents the most serious of all chest injuries, next to the combined thoracoabdominal wounds. Although, as a rule, patients with chest wounds transport well, patients with sucking wounds, unless tightly sealed by dressings or prop-

erly closed by suture, transport poorly. One cannot emphasize too strongly the fact that the most intensive measures at resuscitation are to no avail if an open pneumothorax is not completely closed at the earliest possible time. It must be understood that by complete closure, one does not necessarily imply surgical closure. It is suggested that an adequate means of closure for use in emergencies and until a patient is in condition for surgery is one in which large strips of vaseline gauze are bridged over the open wound and a large gauze pad secured in place over it by the use of tightly applied 3-inch adhesive tape. Packing is condemned. Surgical closure consisting of only through-and-through sutures, or simple airtight closure of the skin, without adequate débridement is to be condemned, because of the high risk of infection, complicating tension pneumothorax, and extensive subcutaneous empyema.

It was observed that in a number of patients with penetrating wounds of the chest who did not obviously exhibit open pneumothorax, if the patients were made to cough while the wound was directly observed, a column of blood (hemothorax fluid) was projected from the wound and open pneumothorax could thus be demonstrated. This clinical test should be carried out on all patients before surgery, as it is most important to determine whether a case is one of so-called "masked open pneumothorax." The type of anesthesia to be used and the operative procedure indicated are directly affected by the diagnosis of the type of injury present.

No patient in shock unless actively bleeding is ever subjected to surgery until after recovery from shock. Following recovery from shock, A-P and lateral

flat plate of the abdomen are taken and patients brought to the operating room. Endotracheal closed anesthesia with positive pressure or controlled respiration technic should be used in all cases, and occlusive dressings not removed until the anesthetist has the patient well controlled. Complete wound excision is done in all cases, and fragmented rib ends resected. Pleural toilet is usually adequately carried out through the débrided wound by the use of rib retractors, or in some cases the wound may be enlarged by incision. Pleural toilet includes aspiration of all blood and clots by suction, removal of bone fragments from the pleura and lung (a common finding), removal of foreign bodies if readily accessible, lung suture, and the instillation of 50,000 to 100,000 units of penicillin (in 20-cc. dilution). An intercostal tube (No. 26 F. catheter) is inserted through the eighth interspace postaxillary line and connected with a water-sealed system. Muscle layer closure is usually adequate in obliterating the open pneumothorax; however, in many wounds of the lower chest the diaphragm must be utilized to effect an airtight closure. Rarely, in very large defects of the chest wall, particularly near the spine, it may sometimes be necessary to suture the lung to the edges of the wound in order to bring about closure. Surgical closure is not done if the wounds are grossly infected, occlusive dressing being used in these cases. Daily thoracentesis is performed to remove pleural accumulations and keep the potential pleural space infection localized.

Postoperatively, these patients receive the same supportive treatment as described under hemothorax. Intercostal tubes are usually removed in forty-eight hours, and daily thoracentesis done thereafter until full reexpansion occurs.

**Tension Pneumothorax**—This infrequent complication of penetrating wounds of the chest equals open pneumothorax as a thoracic emergency. The diagnosis of a tension pneumothorax is not difficult, if the condition is kept in mind. The patient's critical condition makes detailed examination almost impossible; however, the intense dyspnea, bulging relatively fixed chest, tense accessory muscles of respiration, hyperresonant percussion note and mediastinal shift are more than sufficient to establish a diagnosis. A valuable sign for detecting displacement of the mediastinum is that of palpating the trachea in the suprasternal notch and noting its displacement from the midline.

Treatment is simple and in most cases dramatic in effect. A needle of fairly large caliber is inserted into the chest through the second interspace in the mid-clavicular line, which allows the excess air to escape. In continued decompression and for transportation purposes, a flutter valve is attached to the end of the needle, this usually being fashioned from a finger cot or condom. Hospital management usually employs closed drainage with a 15-gauge needle or catheter. Response to this management is sudden and effective, and within a few hours a patient who was virtually fighting for his life is breathing calmly and resting comfortably. Decompression can usually be discontinued within twenty-four to forty-eight hours, except in some of the valvular types, when it must sometimes be continued for days.

Tension pneumothorax resulting from esophageal lacerations requires major thoracotomy for closure of the lacerated esophagus. This procedure is attended with a high morbidity and mortality rate because of the high incidence of mediastinal and pleural space infection associated with this type of injury.

The literature makes numerous references to the development of tension pneumothorax following the closure of open pneumothorax. This complication occurred in only one patient in a personal series of 116 open pneumothoraces.

**Cardiac Wounds**—These are rarely seen in hospital installations, as the greater number of them result in deaths on the battlefield. However, with modern rapid methods of evacuating wounded, some of these patients arrive at forward hospital installations with cardiac wounds. The most common type of cardiac wound seen are those presenting retained metallic foreign bodies of variable size in the myocardium. These patients, aside from showing physical signs of a hemothorax on the left or right sides, are usually in excellent condition. Diagnosis is usually made by fluoroscopic study. Tamponade is usually absent, and when present requires immediate surgery for suture of the associated myocardial laceration.

The management of these cases is a conservative one. Early attempt at removal is rarely indicated. Late removal has been done in a large series with excellent results.

A small number of patients with lacerations of the myocardium have been treated at forward hospital installations in the recent war. Signs of tamponade are usually present and surgery is immediately indicated. These patients require large quantities of whole blood immediately before, during, and after surgery. Heparinization in the postoperative period is effective in reducing the incidence of intramural thrombosis.

### Perforating Wounds

These types of wounds may produce a diversity of effects, such as hemothorax, open pneumothorax, pulmonary

hematoma, massive collapse of the lung, etc.; but, surprisingly, the course of most of these cases is relatively smooth.

In most instances, these patients were wounded by rifle or machine-gun fire.

Patients with open pneumothorax, the result of perforating wounds, may exhibit sucking of both the wound of entrance and exit. It must be kept in mind that although the individual wound may be relatively small in size, the combined wounds may be of sufficiently large caliber as to seriously endanger life, if not adequately closed.

Pulmonary hematomas form an interesting entity. Involving a portion of a lobe and sometimes an entire lobe, they result from interstitial pulmonary bleeding. Hemoptysis is always present in these cases. They are usually not associated with hemothorax, although some of the cases develop a hemothorax (small) twenty-four or forty-eight hours after injury. The course of these patients is usually a very satisfactory one. Other than *wound excision, thoracocentesis*, and *supportive treatment*, no active treatment is necessary.

Management of cases with perforating wounds is similar to that described under penetrating wounds.

### Combined Thoracoabdominal Wounds

These represent the most serious of all war injuries, carrying with them a mortality rate of between 30 to 60 per cent.

Subdivision of these wounds into those of the left and right sides is done for purposes of presenting the more common findings in the lesions and their management.

Shock of a profound nature is the rule in these patients, with hemorrhage the result of liver lacerations as a contribu-

tory and often the etiological factor on the right side, and perforation of a hollow viscus, and/or splenic laceration on the left side. The liberal use of whole blood must be stressed in the treatment of these cases. Unless active bleeding is present, surgery is deferred until recovery from shock has taken place.

Recovery is usually directly proportional to the degree of intraperitoneal involvement. In most patients, wounds of entrance are in the lower portions of the chest, with little resulting damage to intrathoracic structures. Open pneumothorax is probably the most common serious thoracic lesion. Injury to hollow viscera occurs infrequently on the right side.

Left-sided lesions may sometimes present a condition which is termed "tension pneumothorax of peritoneal origin," to denote its etiology. In these cases, wounds of entrance are in the left lower chest, anteriorly with large perforations of the anterior wall of the stomach with a resultant outpouring of a large volume of air into the chest through the lacerated diaphragm. Dr. E. D. Churchill, who was present at the autopsy performed on a patient who exhibited "tension pneumothorax of peritoneal origin," when asked if he thought this condition was possible, was of the opinion that it was with the above-mentioned lesion, although prior to autopsy there had been some controversy as to its feasibility. This condition is obviously not possible in combined wounds of the right side.

One cannot overlook the possibility of "an internal sucking wound" on the left side, in which small quantities of air and intestinal contents are aspirated into the chest during the act of respiration. No matter how small the quantity of air may be, altered intrapleural pressures result with noticeable effect on the pa-

tient. During laparotomy in left-sided combined thoracoabdominal wounds, an "internal sucking wound" becomes a true sucking wound on opening the peritoneum. It must be stressed that next to the control of active hemorrhage, closure of the lacerated diaphragm should be the first duty of the surgeon on opening the abdomen. In lesions of the right side, a sucking wound through the diaphragm is not likely.

In the management of these cases, early operation after complete recovery from shock is imperative, unless active bleeding is present, in which case surgery must often be instituted before shock has been properly controlled. X-ray and fluoroscopic studies of the chest and abdomen are necessary prior to operative interference. Endotracheal closed anesthesia is the method of choice.

Exploration of both chest and abdomen is avoided whenever possible in left-sided lesions; unless a patient presents an open pneumothorax, no surgery is done on the chest other than débridement of the wound. When open pneumothorax is present, débridement and closure are effected with as little intrapleural manipulation as possible.

Transpleural approach on the left side with the thought of doing a single operation is not advised if intestinal perforation is suspected. Complete exploration of the abdomen cannot be carried out through the diaphragm, and the pleura does not react kindly to "leaking" large and small intestine. In a small number of cases where one is reasonably sure that only the spleen may be involved, transpleural approach to the spleen facilitates surgery, and a single operation may in this way be accomplished.

In right-sided lesions, intestinal involvement is the exception rather than the rule, the abdominal damage being

confined to the liver. Transpleural approach in these injuries is always done, with repair of the lacerated liver and diaphragm, the establishment of drainage of the subphrenic space, and the establishment of closed intercostal drainage of the pleural cavity. When laparotomy is necessary, it may be done through a separate abdominal incision or a forward extension of the thoracic incision. Laparotomy is seldom necessary. Drainage of the subphrenic space is an important step in the management of right-sided combined thoracoabdominal wounds, and should be instituted in all cases. Failure to do so may result in a thoracobiliary fistula with empyema.

Postoperatively, shock is treated by the liberal use of *whole blood*, and *oxygen* is administered routinely for at least twenty-four hours. In left-sided lesions, the patients are placed on a routine of (a) nothing by mouth, (b) continued duodenal suction, (c) fluid balance, (d) protein balance, (e) penicillin therapy, (f) large doses vitamin C, (g) periodic blood studies. In right-sided lesions unless laparotomy is performed, patients are able to tolerate full diet within twenty-four hours.

### Blast Injuries

These are closed injuries resulting from the effect of blast on the intrathoracic structures, most notably the lungs. These patients often have associated blast injury to the brain or intra-abdominal organs.

The principal symptoms present are moderate to severe shock, expectoration of large quantities of frothy blood-streaked sputum, dyspnea, cyanosis, pain in the chest, and marked restlessness to maniacal delirium. Physical findings are usually: Increased respiratory rate, impaired resonance to dullness on percussion, usually more marked on one side,

diffuse moist râles throughout both sides, with scattered areas varying to an entire lobe in size over which breath sounds are markedly diminished and of a bronchial nature.

Treatment consists in the use of warmth, *oxygen therapy* (oxygen under pressure preferable) which must in some cases be continued for days, and the judicious use of fluids (*blood and plasma*), particularly in the early phases. *Atropine* has proven of very little value. Double strength plasma has been used with some beneficial effect. The use of *human serum albumin* in 100-cc. doses every four hours for four or six doses gave the impression of being the most effective agent for decreasing the excessive bronchial secretions present in these patients. Sedation is nearly always necessary because of the cerebral symptoms, but it should be used sparingly. *Pantopon* is the drug of choice and should never be given in doses greater than 20 mg. ( $\frac{1}{3}$  grain). *Penicillin* is used routinely to combat pulmonary infection which commonly occurs in these cases. *Cough* and *expectoration* are imperative, as the patients accumulate large quantities of frothy mucus in the tracheo-bronchial tree which favors anoxia by decreasing minute volume exchange.

If surgery is necessary for associated injuries, general anesthesia should be avoided.

### Closed Injuries

These injuries usually result from the recoil of artillery pieces, smashed vehicles, or the impact of any blunt object (large stone or other bomb débris). Multiple rib fractures and sternal fractures are the usual involvements of the chest wall. Intrapleural involvement is one or a combination of spontaneous pneumothorax (unilateral or bilateral), tension pneumothorax, and hemothorax.

Symptoms and physical findings are usually dependent on the type of intrapleural derangement present. Pain and dyspnea are common to all.

Treatment consists chiefly of measures to relieve whatever intrapleural derangement exists. *Intercostal nerve block* is routinely used for multiple rib fractures to enhance cough and expectoration. Multiple rib fractures of the upper anterior chest usually have associated with them paradoxical breathing. The use of *adhesive strapping* or a *sandbag* is usually sufficient to control the paradoxical movements. Sternal fractures with marked depression of a fragment may require open operation and wiring; however, conservative management is preferred, and effective. Elevation of the chest wall by means of traction devices is rarely necessary.

### Retained Foreign Bodies

The management of retained foreign bodies is a subject of considerable discussion in the present-day literature. The types of foreign bodies, size, location, the symptoms produced, and optimum time for removal are important considerations.

The types of retained foreign bodies encountered in war injuries of the chest in the order of their frequency are: (1) Metallic fragments and bullets; (2) rib fragments; (3) clothing; (4) wood (rare); (5) stones, pebbles, and débris (most rare); (6) a combination of two or more, metallic fragments, plus rib fragments plus clothing is a common finding. Most investigators agree that the lung and pleura well tolerate most metallic foreign bodies, but the rib fragments, clothing, and débris are frequently responsible for infection, and that the latter must be removed. X-ray and fluoroscopic studies readily reveal the presence of metallic foreign bodies, but

clothing, most rib fragments, and rubble do not visualize. How, then, is one to determine the presence of these non-opaque substances? Wood and débris, because of their relative infrequency, need cause little concern. The presence of rib fragments, cartilage, and clothing can only be determined by inference based on experience. Almost invariably roentgenological evidence of comminuted rib fractures means spicules of rib in the pleural cavity or lung. The presence of clothing can only be suspected when large, irregular foreign bodies are visualized. Experience has shown that large irregular foreign bodies (2 x 1 cm. or larger) often carry clothing in with them.

The size of the foreign body has a direct bearing on the decision for removal. Large irregular foreign bodies, greater than 2 x 1 cm., are usually removed because they (*a*) often cause cough, hemoptysis, and pain; (*b*) carry clothing in with them; (*c*) cause rib comminution with rib fragments driven into the lung or pleural cavity; (*d*) most often cause large lung lacerations; (*e*) produce a psychosomatic effect on the patient.

The location of a foreign body is of considerable importance because of the complications which may arise. Attempts at removal after complications have developed are attended with great hazards. Foreign bodies located near the great vessels, esophagus, or lying free in the pleural cavity should be removed early. Foreign bodies of small size embedded in the myocardium are usually well tolerated, and may be treated conservatively.

D. Harkens has removed foreign bodies from the myocardium in a large series of cases, with a mortality rate of less than 1 per cent.

Having determined that a foreign body should be removed, when is the opti-

mum time? Carter and DeBakey state "that it has been considered far safer to remove a foreign body in a lung after equilibrium has been established which usually occurs in from three to ten days."

It is the belief of the author, after treating a large series of war injuries of the chest, that there are two optimum times for removal of retained foreign bodies of large size (2 x 1 cm. or larger): (1) At the time of primary operation, and (2) eight to ten or more weeks later. It must be understood that when one speaks of removal of foreign bodies at the time of primary operation, it is presupposed that the patient's condition warrants thoracotomy.

The reasons for removing foreign bodies at the time of primary operation are as follows:

1. General anesthesia must usually be employed for débridement, because the wound is usually too large for excision under local anesthesia, or, as is often the case, open pneumothorax is present.

2. Because of the size of the foreign body, rib fragments (usually), and clothing (often) are possible contaminants.

3. The foreign bodies can be removed with little manipulation, without the need of incising pulmonary tissue, as the fragments are easily and readily removed through a visible wound in the lung.

4. A complete operation is performed including repair of the lacerated lung, with little added risk to the patient, thereby avoiding a secondary operation for late removal.

5. All possible sources of infection are removed, reducing the incidence of infection.

6. The weeks to months of worry and fretting on the part of many patients is obviated (psychosomatic effect).

If it is deemed advisable because of a patient's poor condition to defer removal



of the foreign body, then it is believed that its removal should not be attempted for a period of eight to ten weeks or longer, at which time maximum lung expansion has occurred, infection if present is evident, and if a residual clotted hemothorax is present, it is evident at this time and thoracotomy indicated.

It is believed that the removal of foreign bodies during the so-called period of reexpansion and localization (from the time thoracentesis is instituted, usually the second day, to the time of either maximum expansion or localization of pleural space infection) is contraindicated, because during this time the hemothorax is being emptied, reexpansion promoted, adhesions are forming, and infection if occurring is being localized. To do a thoracotomy at this stage is to invite total empyema.

### Late Complications

These may be summarized as follows:

1. **Clotted Hemothorax or Fibrothorax**—The incidence of this complication is increased after thoracotomy or repair of severe chest wounds, such as open pneumothoraces. Unless adequate provision is made to insure and maintain postoperative expansion of the

lung by keeping the pleural cavity aspirated dry until the exudative phase is over, the resulting fibrothorax will necessitate a second late thoracotomy for decortication. This procedure is usually carried out six to eight weeks postwounding.

### 2. Thoracoabdominal Wounds—

The most common complication is the severe empyema which results following repair of a lacerated diaphragm over wounds of the liver when the latter is not drained subphrenically.

### 3. Empyema—

(a) As noted, thoracoabdominal wounds are frequently thus complicated. Soilage by biliary secretions on the right side and gastric or colonic contents on the left side makes this quite understandable.

(b) Unsutured lacerations of the lung are considered by some to be a common cause of mixed empyemas.

(c) Empyema is more often associated with retained foreign bodies of large size, though under 2 cm. in diameter, there seemed to be little relative difference.

4. **Lung Abscess**—The incidence of early abscess of the lung has been almost negligible.

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## WAR SURGERY

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### INTRODUCTORY

**Mission of Surgical Specialists in the U. S. Army**—In the surgical consultants division, there have been created branches in general surgery, orthopedic surgery, neurosurgery, ophthalmology, otolaryngology, radiation, transfusion therapy, and chemical warfare. The functions of these professional consultant

divisions may be broadly described as administrative, correlative, advisory, educational, and analytical.<sup>1</sup> These consultants are to evaluate, promote, and improve the quality of medical care by every possible means, to interpret the professional policies of the surgeon general, and to aid in their implementation. They assist and advise on the organiza-

tion and program of surgical services in medical installations and the quality, distribution, and proper assignments of professional personnel, provide advice on newer developments in diagnosis and treatment, stimulate interest in professional problems, and encourage educational programs. The creation of specialized surgical centers in the general hospitals in the Zone of the Interior represents another progressive innovation. The program of supervision, coordination, and policy-making has resulted in an equable distribution of surgical talent and a consequent maintenance of a high standard of surgery.

**Current Considerations of War Surgery**—A brief consideration of three years of combat experience shows that definite progress has been made in the surgical care of the wounded. The survival rate among our battle wounded is higher now and the morbidity rate lower than ever before in the history of warfare. The one factor that has contributed most is the high standard of surgery done.<sup>2</sup> This is primarily because of the greater availability of formally trained and well qualified young surgeons and because of their placement by the organization and plan of medical service, where their skill and talent can be utilized most effectively in the early as well as the subsequent care of the wounded. All the experience of the past three years in the management of war wounds has again affirmed the importance of the fundamental principles of good surgery, principles which became well recognized toward the close of World War I and which critically minded surgeons long espoused. New therapeutic adjuncts and basic surgical principles have led to the development of a more rational and effective program of wound management which has provided the most gratifying results yet achieved in military surgery.

**Profits to Peacetime Practice**—The knowledge required for the better treatment of industrial accidents, automobile crashes, train or plane wrecks, or disastrous fires has been not only increased but much more widely disseminated because of the war.<sup>3</sup>

**Emergency Treatment**—The value of protection from secondary infection and the deleterious effect of motion in transport of even soft-tissue injuries have come to be better recognized. The advantages of thorough yet tissue-conserving *débridement* have received fresh emphasis. There has been gained a new concept of traumatic vasospasm as a danger to the circulation of the compromised extremity. *Plaster casings* have assumed their proper place as a measure of protection during transportation. Burns have come to be properly regarded as infectable surgical wounds entitled to full aseptic respect. The damaging effect of escharotics and the value of *pressure dressings* and *non-interference* have been recognized. The advantage of prompt *skin-grafting* has been well learned. In major injuries of the extremities, the surgeon has learned when, how, and where to amputate.

**Bacteriostatic Drugs**—Wartime experience, because of its intensity and extent, has not permitted the development of an attitude of overenthusiastic acceptance of the benefits of *penicillin* and the *sulfa drugs*. They are tools of extraordinary value and usefulness which will greatly supplement but cannot supplant those therapeutic procedures that are based on sound surgical principles.

**Fractures and Bone Surgery**—The advantages of the judicious use of *skeletal traction-suspension methods* of the secondary treatment of fractures have been confirmed. In compound injuries of the joints, the plan of adequate

*débridement, cleansing, suture of the capsule*, and *open treatment* of the remaining wound, accompanied by systemic *penicillin* or *sulfa therapy*, has well demonstrated its efficacy in preventing the dreaded complication of joint sepsis.

**Bowel Surgery**—With the assistance of divided and exteriorized *colostomies* and *chemotherapy*, and with appropriate proximal *decompression*, surgeons have learned no longer to fear for the result in resection and anastomosis of the large intestine. Repeated use of *succinylsulfathiazole* has demonstrated its value to the satisfaction of many surgeons employing it.

**Elective Surgery**—Demonstrable neurologic and roentgenologic demonstrations of protruding intervertebral disk or herniated nucleus pulposus are required as indications for operation. The need for a considerable period of restricted activity has been clearly indicated. In traumatic internal derangements of the knee, the necessity of preserving the stability of the knee joint by meticulous care in protecting the capsular ligaments has been the lesson taught. The value of preoperative conditioning by exercise of the muscles about the knee joint has been demonstrated in promoting earlier recovery and restoration of function after surgery.

**Surgical Complications**—Most surgeons have become convinced of the desirability of intubation drainage in dealing with postoperative pulmonary atelectasis. The early postoperative institution of *bed exercises* and *deep breathing* have shown merit as preventive measures. A better understanding of peripheral phlebothrombosis has been disseminated. Recognition and correction of the contributing causes of bedsores set the stage for their definitive treatment. *Cleansing, protective*

*dressings*, and the *rapid disposal of slough*, sometimes with the help of *urea crystals* or *granulated sugar* or both, prepare the sore for closure by wire sutures after undermining and approximation of the skin edges. Systematic administration of *penicillin*, before and after operation, contributes to the complete and clean healing.

**Materials**—Serum albumin, fibrin foam, fibrin film, and thrombin-fibrinogen glue have resulted from the fractionation of blood proteins. Tantalum has been popularized as a nonreactive, electrically inert, yet strong and workable, material as wire for sutures, plates for bone defects, and foil for protection of delicate tissues. The general use of nonabsorbable sutures of wire, cotton, and silk has won many converts.

**Supportive Measures**—There has been developed a fresh appreciation of the importance of certain supportive measures to be employed not only as a postoperative procedure and in protracted illness, but as a means of prevention of deterioration and as a means of preoperative preparation. New emphasis has been placed on the necessity of *forestalling and controlling vitamin deficiency states*. The importance of *maintaining nitrogen balance* is now more fully appreciated and the means for correcting its lack are at hand in *plasma serum, albumin*, and the *amino-acid preparations*.

**Reconditioning**—It is the universal impression that *bed exercise*, both general and special, has hastened recovery, shortened bed rest and hospitalization, and tended greatly to diminish the incidence of pulmonary and thrombotic vascular complications. Exercise and increasing *directed physical activity* after the patient has left his bed have proved so beneficial as to throw into sharp contrast the general neglect of

such measures in the past. Recreation, instruction, amusement, the development of new skills and hobbies, the stimulation of new interests, and a new outlook have played a large part in reconditioning. The importance of this phase of rehabilitation can hardly be overemphasized, and should be carried over into civilian practice.

**Mistakes in War Surgery<sup>4</sup>—Abdominal Wounds**—The slow administration of intravenous fluids when their remedial effect is urgently needed is an anachronistic carry-over. Holes in the small intestine should be closed transversely with avoidance of resection if possible, but if the closure of a defect in the small intestine narrows it unduly, the insertion of a small rubber tube into the lumen will keep this open until edema subsides. When a V-shaped defect is present in the small intestine and it is feared that closure will result in undue narrowing of the lumen, the wedge may be widened by excising the sides of the V so as to increase the acute angle. Closure then results in a lumen which is larger than it was before the wound was incurred. When resection is necessary, cutting the bowel obliquely will avoid undue narrow of the gut when an end-to-end anastomosis is to be used. All wounds of the colon should be exteriorized and a *double-barreled colostomy* done with the afferent and efferent loops sutured together after the method of Mikulicz. A wound of the rectum should be treated by *débridement, drainage, suture of the bowel* when possible, and a *double-barreled sigmoidostomy*.

The postoperative care of the patient is as important as the actual operation and his safety is furthered by tube decompression of the gastrointestinal tract. Parenteral administration of *adequate fluids* and *sulfa* is important. The bene-

fits of removal to a rear area are overrated and should not outweigh the well-known dangers of moving a recently operated patient.

**Wounds of the Lower Extremity—**

An effective *tourniquet* should be applied immediately. Palpation along the course of the femoral artery distal to the tourniquet will demonstrate whether arterial flow has been stopped. Suturing of the main knots of the tourniquet with strong suture material insures against slipping and this should be done when bleeding from a large artery is suspected, especially when a person is covered with oil. The trauma of packing wounds lessens the chance of survival and does not help stop the bleeding. The vessels involved should be exposed and clamped or occluded by manual pressure.

**Application of Principles**—There are no correct methods in war surgery.<sup>5</sup> There are established principles, but the way in which those principles should be applied varies with time, place, and circumstance. The terrain in which the campaign is being fought; the climate and the time of year; the severity of the action, its success or failure, and the speed of advance or retreat; the weapons principally employed; the prevalence of disease among the troops and the state of exhaustion, dehydration, exposure, and mental strain of the soldiers when wounded; the time lag between injury and first aid and between first aid and arrival at an organized surgical center; the conditions under which these centers are working, their housing, their light and ventilation, their supplies, their exposure to air attack, their complement of orderlies and nurses; the number of casualties arriving at a time; the length of the lines of evacuation, the smoothness of transport and the facilities for supervision during the journey, the spacing and adequacy of medical units on the

way; the distance of the centers of definitive surgery and their establishment in beds and personnel in relation to the numbers reaching them.

**Preparation of War Casualties**—Beecher<sup>6</sup> discusses the immediate physical consequences of the wound and the inseparable mental and emotional problems that arise from it, in terms of what is needed to prepare the wounded man for surgery. Specifically, the distress of the wounded man was found to come from three sources—pain, mental agitation, and thirst. Severe pain is usually best treated with *morphine*; but much that has passed for a response to pain was found to respond to small doses of *barbiturates*. Pain great enough to require further treatment with morphine was found to be surprisingly infrequent (present in only one fourth of the severely wounded as they arrived at the most forward hospital). A great need was found in the newly wounded man for the use of small doses of sedatives of the barbiturate type.

The relationship of the wounded man to those around him, especially the physician and the chaplain, is discussed, with a view to preparing the man for his future care.

The effect of adverse external circumstances upon the wounded man and his course along the evacuation chain are discussed with attention being given to details of the organization and application of supportive treatment which must precede the initial surgery. One clue to the extent of the resuscitative measures that must at times be carried out is to be found in the fact that even in the most forward hospitals, the field, and the evacuation hospitals, the average duration of operation for craniotomy, laminectomy, celiotomy, and thoracotomy was of the order of two hours or more (not including anesthesia induction

time). Even operations upon the extremities averaged more than an hour. The deliberation in the surgery carried out compares with that of peacetime medicine.

Experience has shown that about 2.5 per cent of battle casualties (under the conditions of study) will require intensive resuscitative measures. The needs of this desperately wounded group are discussed from three points of view: (a) Treatment of the local wound. Surgery is an inseparable part of resuscitation in its broad sense. On occasion there can be no resuscitation, even temporarily, without surgery (*cf.* internal bleeding, great fecal contamination of the peritoneum, etc.). In any case resuscitation (*blood therapy*) should continue during and after surgery. (b) Treatment of the depleted circulating blood volume. Here, position of the patient, gastric distention as it interferes with the circulation, application of heat, and *oxygen therapy* are all discussed. Route of administration of fluids, the rôles in therapy of saline and glucose solutions, of plasma and albumin preparations, and of whole blood are considered in detail. In the case of blood administration, problems and hazards concerned with volume and speed of administration are dealt with. (c) The treatment of pain and emotional disturbances is discussed.

The timing of blood administration and its relationship to the optimum time for surgery are mentioned, as is also the question of slow against rapid preparation for surgery.

**Casualty Handling Afloat**—Casualty handling in the hot, humid quarters of a ship's sick bay presents the medical officer with a characteristic series of "bottlenecks."<sup>7</sup>

A "check-off" list can be used as the ship approaches the operational area.

Lack of uniformity in craft carrying casualties must be anticipated, and plans made to unload any variety of boat. As patients are sorted in the "collecting station," x-ray films and descriptive diagnoses should be made to avoid unnecessary rehandling. The utilization of "clean-up" tables will expedite the preparation of patients for dressings and operations. A simple transfusion set is described, together with the duties of the transfusion team. Attention to hemostasis and the application of skin traction at the time of guillotine amputation will save the patient unnecessary transfusions and early painful dressings. Wound débridement can proceed while casualties are being prepared for major operations. Packs in open débrided wounds are seldom indicated. Adequate immobilization of fractures with padded casts, splints, and skin traction is usually preferable to the more time-consuming attempts at reduction. Definitive treatment of fractures can be delayed until evacuation to a hospital. When urinary sediments cannot be watched, *sulfonamides* by mouth had best be discontinued at the end of 72 hours. Large doses of *alkalis* are necessary to change the reaction of the urine. More time and care should be spent on the original dressing done aboard ship. Wounds dusted with *sulfanilamide powder* should be dressed with a sterile ointment on the third day. Records and roentgenograms should be kept on the person of each casualty when he is evacuated.

**An Air-borne Surgical Center—**Goligher and Wells<sup>8</sup> examine the type of medical service provided for an air-borne force and explain the rationale of an air-borne surgical center in the larger air-borne operations. They conclude that gliders are essential to bring in the greater part of the equipment

needed, together with jeeps to carry it on the ground. They describe the type of building to be selected and its preparation for use as a surgical center. Internally, it is divided into the following departments: Reception, resuscitation, theaters, wards, kitchen, and general. They strongly advocate using *fresh blood*, obtained from members of the air-borne force itself, due to the difficulty of utilizing stored blood for transfusion purposes in air-borne surgery. These recommendations are based upon experience in establishing four air-borne surgical centers.

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## SHOCK

**Cause—**From a series of limb trauma experiments, Phemister and Laestar<sup>9</sup> concluded that where shock developed the local blood loss was large and constituted the outstanding causative factor. The maintenance by spinal anesthesia of a blood pressure low enough to limit hemorrhage to an amount too small to produce shock is contraindicated in man as the amount of anesthetic required would be too toxic. Indications for the use of local or spinal anesthesia in shock are based on grounds other than the blockage of afferent nerve impulses.

**Shock from Burns and Trauma—**Fox and Keston,<sup>10</sup> in experimental work, found that the sodium content of injured skin and muscle is greatly increased and exceeded the gain in water (edema). This indicated that additional sodium accumulated in the intracellular compartment. As a result of the redistribution of sodium and water, approximately one half the total amount of extracellular sodium was sidetracked and rendered unavailable. Administration of this amount of sodium by injection of 0.9 per cent sodium chloride containing radiosodium was followed by

nearly complete retention of sodium in the injured animals but by excretion of sodium in normals. The relationship between the reduction in plasma volume characteristic of shock and depletion of extracellular fluid is discussed.

**Wound Shock**—The syndrome of traumatic shock due to wounding by high explosive missiles was notable for its variability.<sup>11</sup> Reduction in blood volume was a characteristic finding. Hemoconcentration as evidenced by elevation of red cell hematocrit or plasma protein above normal ranges was not encountered in the absence of burns or complicating clostridial myositis. Despite restorative therapy, anemia and hypoproteinemia were the rule during convalescence. Quantitative improvements in blood volume and in concentration of plasma protein and hemoglobin did not occur in response to replacement of plasma and blood. No evidence of overdosage in plasma and whole blood therapy was detected. Dehydration and azotemia were common in early convalescence. In fulminating clostridial myositis with edema, plasma protein concentration and blood volume fell rapidly. Erratic effects were obtained from *sulfonamide therapy* if the concentration of the drug in the blood is significant. Base deficiency, when present, was of mild degree as evidenced by the urinary reaction. The effectiveness of the surgical management of this selected group of the gravely wounded is attested by the low mortality rate during the period of observation.

**Treatment**—"Lightly and heavily" degraded *gelatin solutions* have been employed as a substitute for plasma in the treatment of shock caused by trauma or severe burns (trauma, 67 patients; burns, 28 patients). Lightly degraded gelatin solutions seem to be retained longer in the blood stream, and appear

to be as effective and safe as plasma in the management of these types of clinical shock.<sup>12</sup>

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## BURNS

### Treatment

**Whole Blood Therapy**—It is difficult to compare the effectiveness of blood and so-called blood substitutes.<sup>13</sup> For this reason, some of the observations cited might best be termed clinical impressions. In the experience of Evans and Bigger, if fairly large amounts of *whole blood* are given to the burn patient during the first forty-eight hours "masked anemia" is not encountered, whereas this condition occurs frequently in patients treated only with plasma. Thus, secondary anemia in burn patients may be more easily prevented than treated. When burn patients are given plasma alone, even in large amounts, it is not unusual to find low plasma protein levels on the fourth or fifth day. In those treated with large amounts of whole blood, the plasma protein levels were maintained at more nearly the optimum level. Thus, one of the advantages of whole blood therapy may be the maintenance of the liver in such a state that plasma protein production is carried on in a more nearly normal manner during the initial burn period. It was found possible to maintain a good urinary output even when hemoconcentration appeared to be quite marked. An attempt should be made to induce the burn patient to take fluids and food (especially protein) *by mouth*, so that it is not necessary to give large amounts of fluid intravenously. It is the clinical impression that burn patients treated with whole blood have shown less toxemia than did other patients treated with plasma or gelatin. The

authors were pleased with the rapidity with which growth of epithelium took place in burned areas that at first appeared of a depth and extent to require extensive skin grafting. Only with an adequate circulating red cell mass can oxygen and food, such as amino acids, be carried to the zone of injury in sufficient quantities. There was no instance of thrombophlebitis or pulmonary embolus clinically recognizable. Experience, then, indicates that whole blood can be given safely to burn patients in the presence of moderate to severe hemoconcentration.

#### **Skin Grafts—Selection of Time—**

A period somewhere between the second and third weeks after an extensive deep thermal burn is likely to prove the optimum time for excision of nonviable burned tissues and the immediate application of skin grafts of intermediate thickness. The dissection is difficult and small amounts of viable tissues may be removed inadvertently. On the other hand, morbidity is reduced considerably, and recovery apparently is earlier.<sup>14</sup>

**Full Thickness Grafts from the Neck**—Full thickness grafts from the neck and the clavicular region have been found to give superior results in the repair of facial defects.<sup>15</sup> Two main advantages are improved function and color; another is softness and, therefore, function.

**Technic**—The scarred or deformed area is dissected free and the edges are moved back to their normal position carefully, so that they are not undermined or too irregular and so that an accurate fit (or set-in) of the graft can be done. With this excellent graft available, careful dissection can be done and repositioning of parts fully carried out, with the thought of accurately filling the defect and counting on only the slightest contracture of the graft bed. The pattern of the defect, in pliofilm or celluloid (roentgenogram film), is marked out usually just above the inner third of the clavicle either with methylene blue or directly with the

knife. The graft is removed in the usual manner, with good firm stretching by assistants to produce a "drumhead" to work on. After an edge is freed, fingers are used to hold the graft instead of forceps or hooks and the dissection is completed carefully at the proper full thickness depth so that no trimming of the undersurface of the graft has to be done later. These grafts appear so thick that their growth might seem questionable, but growth of them has been as good as of split grafts, and there has been none of the spotty necrosis sometimes seen in full thickness grafts.

Donor sites are usually closed, or are partly closed and partly left open, or covered with a split graft. The grafts are set in accurately with interrupted sutures of light silk, every 2 to 4 mm. around the borders. The ends of the sutures are left three to four inches long for subsequent fixation of a waste form, and each two sutures are clamped with a mosquito clamp. No holes are cut in the graft. The graft is covered with fine mesh grease gauze and a wad or form of white cotton mechanics' waste is packed carefully over this to assure firm coverage of the entire graft. Appropriate opposite sutures in pairs are selected for the first anchorage, and, as the assistant firmly compresses the waste with his fingers or instrument, these opposing sutures are firmly tied over the waste in pairs. The eye is protected with a suture closing the lids if necessary, and usually a larger over-all waste pressure dressing is applied, with a gauze roll going around the head to obtain counterpressure posteriorly. This fixes the whole area and is usually more comfortable than just the small waste form without further fixation.

Dressings are done on the third to sixth day, and subsequent ones are repeated as necessary, usually having them off about the tenth day.

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## **SOFT TISSUE INJURIES**

### **Amputation**

**Early Care of the Amputation Patient**—Danger to life and the future uselessness of the extremity are the indications for amputation. Questions to be decided are: (a) Is the blood supply irreparably damaged? (b) Is the infec-



tion uncontrollable? (c) Will the limb be useless? Initial amputation is provisional and should be of the open type. The technic of the modified guillotine procedure with slight variations in certain cases has been described. The importance of traction in the early management of amputation cases has been emphasized and its maintenance during transportation has been stressed.<sup>16</sup>

**Surgical Management—Evaluation of Stump**—For the first ten days after admission, the patient is built up nutritionally and his general condition studied and evaluated. Anemia, hypoproteinemia, malaria, and other complications are attended to by *blood transfusion, high protein diet, and appropriate medication*. *Traction* is applied immediately to all stumps with open wounds and simple vaseline gauze dressings cover the wound surface. During this probationary period, the stump is also carefully evaluated. Roentgenograms, bacteriologic studies, sketches, and photographs are made showing the progress of wound healing, and the first definitive procedure is planned.

**First Definitive Procedure**—The aim is to obtain a healed stump. As a result of prolonged skin traction, a concentric scar firmly attached to the underlying bone is obtained. Skin grafting produces a healed wound but the scar may be too fragile and break down in the ordinary case. Modified flap amputation is followed by a scar that is generally depressed or puckered. None of these scars are adequate for the support of a prosthesis. Their fragility and position make it difficult for the amputee to wear his prosthesis. For this reason a further and final step has to be taken.<sup>17</sup>

**Second Definitive Procedure**—The aim following plastic repair, revision, or reamputation is to leave the best pos-

sible stump and one of the greatest length obtainable. It should be of the shape that allows it to be fitted properly with an artificial limb. The tissues at its end should fit snugly, neither loosely nor too tightly. It should consist of nothing but skin and subcutaneous tissue. There should be a minimum of scar tissue in the stump, both superficially and in its deeper portion. The scar should be so placed that it is away from the pressure of the artificial limb. It should not be adherent to the end of the bone.

There has been general agreement on the desirability of obtaining as a final result one of four types of amputation. These four types are the Syme's amputation, the below-knee amputation, the Stokes-Gritti amputation, and the mid-thigh amputation. While a modification of these four types may be indicated under special conditions, these standard amputations have met the demand of the average case.

**Aftercare**—Two further duties remain to be performed. The surgeon must prepare the stump to receive the prosthesis and he must teach the patient to use it. Preparation of the stump means that the shape of the stump must be changed in order that it may be fitted properly with an artificial limb. The bulbous or edematous stump must be shrunk in order that it may become a narrow cone. This is done by the compression obtained from a *tight elastic bandage* that has been previously unwound and stretched. Shrinking is also obtained by the wearing of a pylon. Bandaging has the advantage that it can be started early, long before the stump can tolerate the pylon. The bandage is applied under great tension to the end of the stump, otherwise the stump becomes bulbous instead of conical. Band-

aging is repeated several times a day, and, if rigidly followed, sufficient shrinking in from four to six weeks is obtained so that a permanent prosthesis may be applied. This goal is rarely reached without close scrutiny and supervision.

**Massage** of the stump is contraindicated. **Physical therapy** has no place in the aftercare of amputation stumps except in the management of contractures and in the employment of exercises. These latter are required in thigh amputations, especially in short thigh stumps. The loss of the distal attachment of the adductor muscles causes overaction of the abductors. Development of the adductors and extensors of the hip is necessary in order to control the use of the prosthesis. The loss of the knee mechanism puts a double load on the hip extensors, that of extending the hip and the artificial limb.

**Plastic Surgery of Amputation Stumps**—The open amputation stumps resulting from guillotine amputations are surgical ulcers and should be covered at the earliest possible moment in which the stump bed will accept a graft. The application of *skin traction* will help to draw the skin gradually over the end of the stump until the wound heals with a deep concentric scar. This procedure, however, requires considerable time. **Skin grafting** reduces the period of treatment and many other advantages result.<sup>18</sup>

Prior to the application of the skin graft, edema must be eliminated, vasomotor tone and local circulation improved, and infection diminished. Postural treatment aids in this and can best be accomplished by keeping the patient strictly in bed and elevating the part. Pressure dressing and local compresses stimulate the ulcer bed to develop firm, flat granulations. The control of local

infection is best obtained by the use of 100,000 units of *penicillin* two days previous to skin grafting and for at least seven days after operation. *Sulfadiazine* as an adjunct is of value, particularly where staphylococcus infection is present.

**Method of Application**—The one-piece, thin, split-thickness skin graft is easier to handle, has a better chance of survival, and provides adequate skin coverage. Through the continuous contraction of the skin-grafted bed, more of the adjacent skin is mobilized, facilitating later revision of the stump. The split-thickness graft is perforated throughout to permit drainage and is then sutured to the margin of the wound under normal skin tension. The graft is further secured to the wound by many basting sutures.

**Aftercare**—The final dressing may be open or closed. The relative percentage of "takes" with both types of dressing has been the same. If the ulcer is relatively clean and the bed regular, the closed method is preferred. When the base is irregular and exudation more active, the open method is employed.

**Closed Method**—This consists in applying several layers of 3 per cent xeroform gauze to cover the graft after it has been sutured to the new bed. Flat gauze sponges and a large flat gauze pad are placed in position and held firmly in place by elastoplast. Anterior and posterior skin traction strips are now placed in position and a firm elastic bandage is applied. The grafted area and its proximal joint are immobilized by splinting. The entire area is elevated and not disturbed for five days. On the fifth day all of the dressings are removed. Secretions are evacuated and a similar dressing and splint reapplied. This dressing is changed on the tenth postoperative

day. All the sutures are removed, secretions wiped away, a dry pressure dressing reapplied, and traction is continued.

**Open Method**—It is necessary to use many more basting sutures, as these are the main points of graft immobilization. Skin traction with a 3-pound weight is applied and a plaster cast is added to immobilize the proximal joint and to

discarded and a mild pressure dressing is applied and traction employed for another week. All dressings are then removed but the traction is continued.

**Revision of Thigh Amputation**—The first step is to excise the disk of scar tissue on the end of the stump. The skin flaps are then mobilized. The bone and muscle are shortened sufficiently to

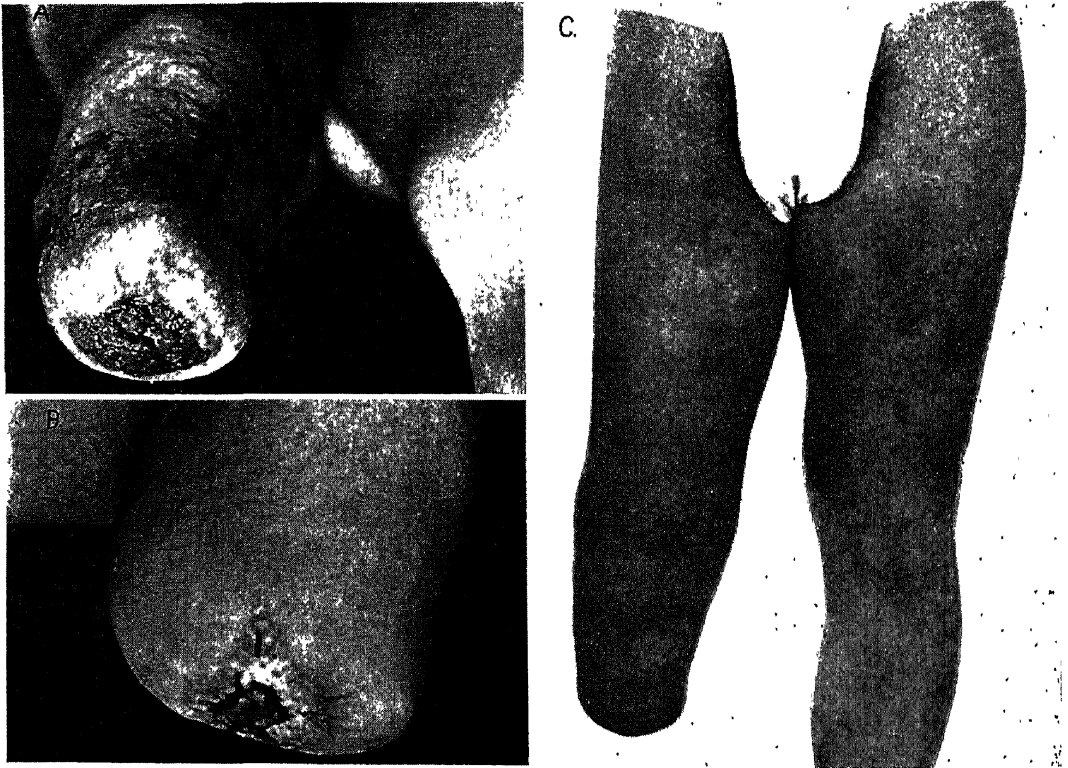


Fig. 1—*A*, Guillotine amputation below the knee with short stump. *B*, After skin-grafting and contraction of the scar area. *C*, Revision of stump without bone loss, preserving knee. (O'Connor, G. B. and Kessler, H. H.: U S. Nav. M. Bull. 44: 1169 (June) 1945.)

protect the grafted area. The cast is so constructed that the grafted area is open but protected by plaster strips. The part is elevated and, by using sterile applicators and massage from four to eight times a day, the secretions that collect are removed. The massage is done from the center to the periphery, forcing the secretions from under the graft. The sutures are taken out on the tenth day. On the fourteenth day, all splints are

permitted the skin to be closed over the end. A tourniquet may be employed, but only briefly. The bleeding points are secured with absorbable sutures and the nerve is severed and permitted to retract. The periosteum is cut cleanly and the femur is severed. If undue lateral prominences of skin exist, they are trimmed before closure. However, the objective is to get a rather square stump, and not to jeopardize the blood supply of the skin

flaps by carrying the incisions too far proximally.<sup>19</sup>

**Reamputation**—The principles are the same as those for a primary flap amputation.

**Technic**—The anterior skin flap is laid out a little longer than the posterior flap so that the resulting scar will lie posterior to and not directly over the end of the femur. Laterally

The nerve is severed and allowed to retract into a cushion of soft tissue. Ligatures around the nerve are to be avoided even at the expense of a little bleeding. The flap is closed over the end of the wound. Should sulfonamides be desired locally, the drug of choice is *sulfanilamide*, as it is absorbed with sufficient rapidity so as not to interfere with wound healing. *Sulfathiazole* and *sulfadiazine* are better given by mouth.

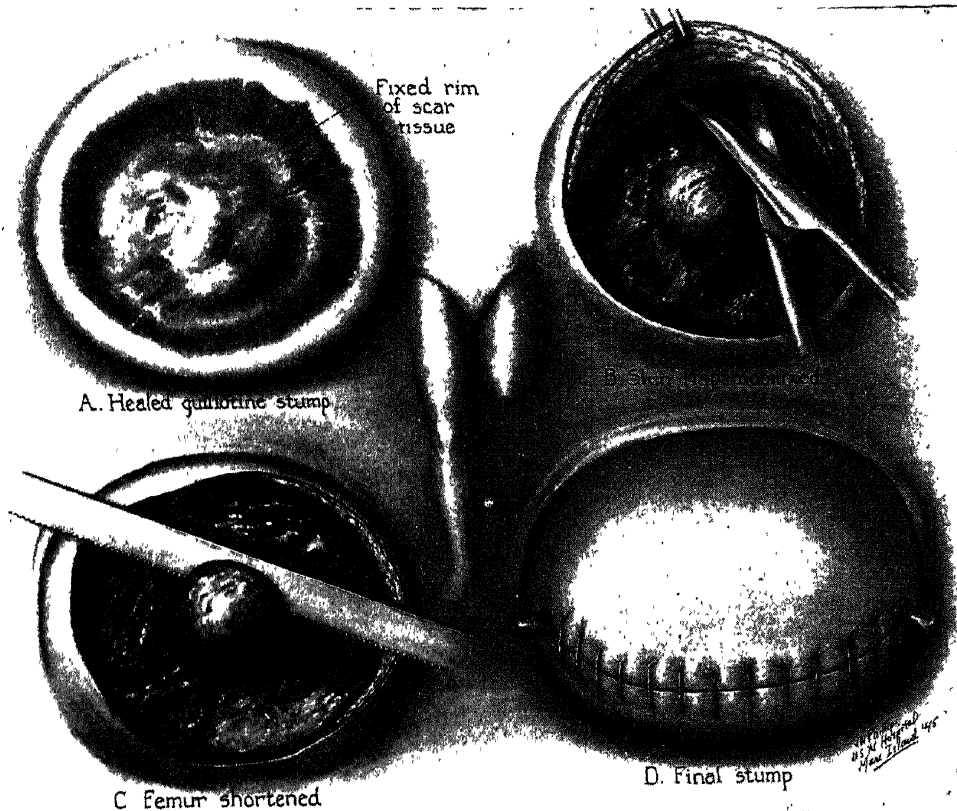


Fig. 2—Revision of thigh stump. (Olson, P. F.: U. S. Nav. M. Bull. 44: 1181 (June) 1945.)

the incisions do not extend proximal to the level at which the bone is to be severed, the purpose being to insure a good blood supply to the central portion of the flap. The incision is carried deep, including the fascia with the skin. The flaps are dissected back and the muscles and bone cut across squarely. Muscle is not permitted to extend distal to the end of the femur. Because of its retractility, however, it may be severed at a slightly distal point. The blood vessels are secured with catgut ligatures, since nonabsorbent suture material is not well tolerated in proximity to muscle and is apt to cause irritation under weight bearing.

**Postoperative Care**—If left to himself, the patient will seek the most comfortable position and will soon have the thigh stump propped up in acute flexion. The raw muscle ends reattach themselves to the surrounding tissue, and if the stump heals in a flexed position, a contracture in that position will result. It is therefore imperative to keep the stump in a neutral position. Perhaps the best way to accomplish this is to apply skin traction while the patient is

still anesthetized and to continue the traction until the wound is healed. As soon as the stump is healed, *physical therapy* is instituted for the purpose of developing mobility and strength of the thigh stump in the directions of adduction and extension. The amputees who walk least well are those who have abducted and flexed thigh stumps. Such

vide a painless and comfortable adjustment to an artificial leg.

**Procedure**—When a patient is admitted, the stump and wound are carefully studied and measured. Photographs, sketches, and roentgenograms are made. Routine laboratory and dietetic measures are instituted, and a general evaluation of the patient's condition is made. A program of dressings, traction, and general care is outlined and followed. All preliminary treatment aims at wound closure. Before final revision is performed, the stump should be closed and dry. The percentage of failure to obtain an ideal stump is increased by hurrying into a revision before proper closure of the wound. Occasionally all attempts to close the wound will fail and a revision will be performed in the presence of an open wound. This is done only when inflammation and edema are reduced to a minimum. Closure of the wound may usually be obtained by traction and split-thickness skin flaps for closure. When the wound is closed, dry, and all scabs and débris have had time to be removed, the stump is prepared forty-eight hours preoperatively and the patient is brought to surgery for his final revision.

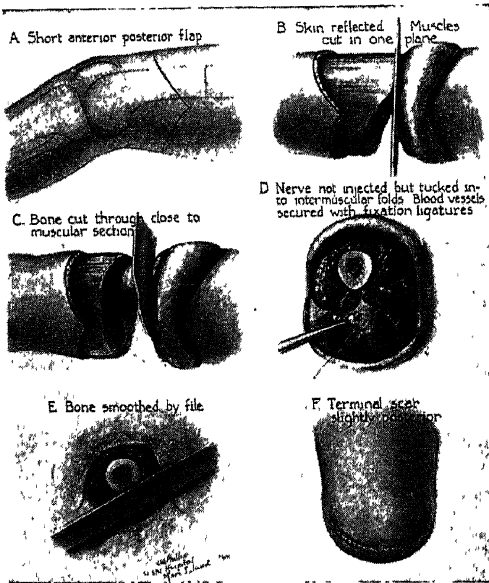


Fig. 3—Reamputation of thigh. (Olson, P. F.: U. S. Nav. M. Bull. 44:1183 (June) 1945)

patients will walk with a waddle gait because of the abduction, and with a sway back because of their inability to get the leg underneath and behind them. These defects can be guarded against by leaving the thigh stump long, by preventing flexion contracture during convalescence, and by instituting early and vigorous exercises.

**Revision of Below-knee Amputation Stumps**—The stumps vary greatly in length. The primary objective has been to save bone length and not to select an ideal site for amputation.<sup>20</sup> The ideal is to obtain a stump of such shape, length, and condition as to pro-

**Operation**—Below-knee operations are facilitated by placing the patient on his abdomen with a small triangular block or folded sheet elevating the leg. Spinal, intravenous, or general anesthesia may be used as preferred. Methylene blue or a similar dye is used to mark the lines of skin incision. The author rarely uses a tourniquet; manual pressure on the femoral artery has proved satisfactory for control of hemorrhage.

The flaps should be semicircular rather than oblong. The perimeter of the anterior and posterior flaps should be as nearly equal as possible in order to prevent dimpling. The flaps should be equal in length, since the stump will not be an end-bearing one. However, a slightly longer anterior flap resulting in a slightly posterior scar is satisfactory. Short flaps should be made with enough bone resected

to allow loose coverage of the bone antero-posteriorly. The short flap destroys less circulation, with less marginal necrosis and slough. The resulting medial and lateral prominences, dog-ears, may be removed after healing by wrapping or plastic operation. The center of the wound is the area where necrosis and sloughing ulcers are most frequently seen. Once this area is healed, dog-ears are easily removed.

With the proper preparation and markings completed, incisions are made through the skin and deep fascia down to the muscle. These flaps are made in healthy skin, allowing for excision of the existing scar. The skin and deep fascia are cut down to the muscle. The skin and deep fascia are undercut and rolled upward and held out of the operative field by a single suture anteriorly and one posteriorly through the skin. Anteriorly the fascia and tibial periosteum fuse and the subcutaneous tissue is more sparse than posteriorly. However, there is enough tissue to allow for a row of sutures in the subcutaneous tissue at closure.

Anteriorly the muscle is cut with an amputation knife at right angles to the bone at a point about one-half inch from the rolled cutaneous flap. Posteriorly the muscle is cut at an angle of about 55 degrees with the bone from outside inward and distally to the point one-half inch distal to the level at which the bone is to be sectioned. This oblique posterior incision of the muscle aids in the attainment of the conical shape desired.

A circular incision of the periosteum is made one-quarter inch above the level at which the bone is to be sectioned, and the periosteum is scraped distally with a periosteal elevator. The tibia is then sawed through at a point one-quarter inch distal to the point of circular incision of the periosteum, thereby leaving about one-quarter inch of bare cortex. This decreases periosteal trauma in the beveling process and lessens the tendency for formation of exostoses. The fibula is sectioned at a level one inch to one and one-half inches above the level at which the tibia was sectioned by means of a Gigli saw.

The vessels are now ligated with suture ligatures. Nerves are best left alone or gently pulled out a short distance and severed with a very sharp scalpel or razor. The tibia is beveled and the sharp points smoothed down with a coarse file. Relative hemostasis is assured. Deep drains are placed at both ends of the wound. The subcutaneous tissue is carefully sutured with chromic catgut. The skin is closed with a dermal-type suture and the wound is dressed.

Skin traction with adhesive strips is applied at once. This removes tension from the suture lines and aids in prevention of flexion contractures of the knee. The patient is given as a routine procedure one day of *sulfadiazine* and *penicillin* therapy preoperatively and seven days of each postoperatively.

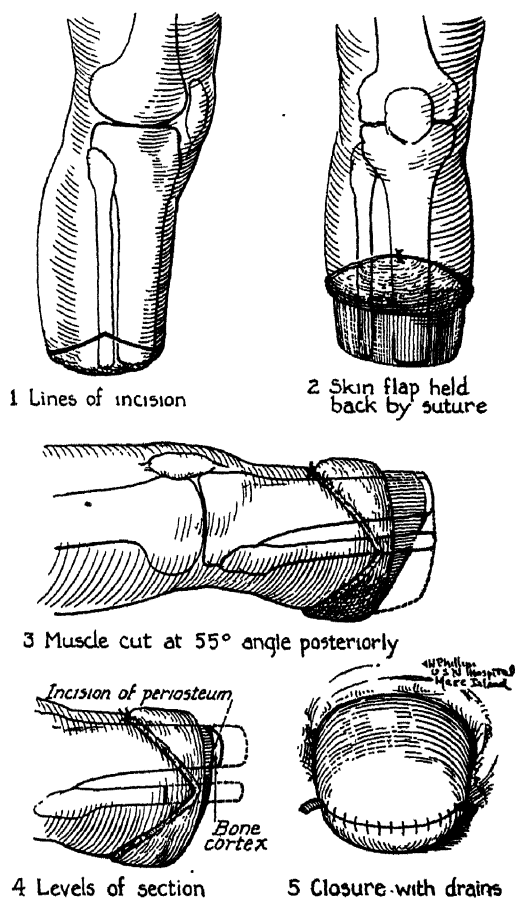


Fig. 4—Reamputation below the knee. (Nesting, O. S.: U. S. Nav. M. Bull 44: 1191 (June) 1945.)

**Complications**—Hematomas are rare because of the careful hemostasis performed at operation and routine drainage of the wound. Postoperative infection has been minimized by performing revisions only after wound closure, by use of *sulfadiazine* and *penicillin* therapy, by infrequent late dressings postoperatively, and by insistence that all personnel applying wound dressings wear masks, gloves, and gowns. Feeble healing and marginal necrosis are combatted

by the use of short skin flaps, loose approximation of skin flaps anteroposteriorly through resection of adequate bone length to insure that result, and fourteen days' elevation of the stump by keeping the patient in bed. Postoperative pain is rarely a serious complication with adequate drainage, reasonable use of narcotics, elevation of the stump, and care in not applying too tight a dressing. Flexion contractures of the knee are rare, if constant traction is maintained, with early physical therapy. Neuromas and painful stumps are infrequent because of minimum traumatization of the nerve ends at surgery, drainage of the wound, careful suture of the subcutaneous tissue, thereby decreasing adhesions between skin and underlying soft tissue, and careful fitting of the stump to a prosthesis.

#### Treatment of Painful Stumps—

The most common site for a painful stump is in the amputated finger, and the treatment of the commonly found medial and lateral neuromas is one of *incision*, usually performed by the plastic surgeon. The number of painful stumps is in direct relationship to the technic employed in handling the nerve trunks at the time of the initial or secondary operation. The following steps are advantageous in lessening painful neuromas:<sup>21</sup> (1) Only slight traction on the nerve trunk during the operation; (2) severance of the trunk as high as is practicable, with little traction, with a sharp scalpel; (3) no injections of the trunk with alcohol or other chemical agents, and (4) covering the end of the nerve trunk with muscle whenever possible without appreciably altering the course of the nerve.

Another procedure has been to divide the involved nerve trunk proximal to the neuroma and covering the proximal end of the nerve with a tantalum cup,

holding the latter in place with two or three fine tantalum wire sutures passed through the sheath. This protective covering (1) minimizes the amount of scar formation in the end of the nerve, (2) prevents scar from adjacent tissues from invading the nerves, and (3) protects the future bulbous end of the nerve from the irritation of external stimuli. The cup is rigid and is large enough to prevent constriction of the blood supply in the nerve.

**Compression Dressing of Amputation Stumps**—After guillotine amputation, the distal skin edges are grasped with several towel clips or the subcutaneous fascia may be grasped with hemostats. With these the stump is held up. The part is then painted with *tincture of benzoin* or with *ace adherent* if it is available. Starting at the joint proximal to the amputation, three overlapping turns of a 3-inch elastic bandage are made under the amount of tension necessary fully to stretch the bandage. The bandage is then carried distally, overlapping two thirds of its width on each turn so that three layers are applied up to the skin edge.<sup>22</sup> A piece of felt or other padding may be placed over the proximal end of the adductors of the thigh, or over the tibial crest or head of the fibula, to prevent too much pressure, but if the bandage is not applied too tightly this will not be necessary. A 2-inch strip of adhesive tape is placed around the proximal end of the bandage to prevent its rolling down the stump. This step is very important. At this point the end of the stump is usually definitely cupped. The clips are removed and if the bandage has been properly applied, no retraction takes place. A separate end dressing may be changed as often as necessary without disturbing the compression bandage.

If such a dressing is applied at the time of amputation, edema does not develop and the closure is rapid. If applied after edema has a start, there will be profuse serous drainage until the edema is reduced. This necessitates frequent change of the end dressing and earlier reapplication of the compression dressing. There is some discomfort for from thirty minutes to an hour if the bandage is applied several days after amputation, but after this it is very comfortable. The patient can be moved and can shift position easily. He will soon be able to be up in a wheel chair or on crutches. This is mentally and physically beneficial. A compression dressing with the readily available elastic bandage has proved ideal under field conditions, and it offers many advantages over traction for use anywhere.

### Crush Injuries

**Pathology**—The similarity of the pattern of pathologic findings in five cases autopsied indicates the pathology of immersion blast injury. There was absence of external evidence of injury which could be ascribed to the blast.<sup>23</sup> The muscles of the chest wall and abdomen showed no signs of hemorrhage or trauma. The traumatic lesions were apparently limited to air-containing organs, and it is significant that air-inflated rubber life belts also ruptured as a result of the blast. This damage was similar in nature to that which was suffered by the intestines and lungs, which were the only organs receiving any direct injury as a result of the underwater blast. The most serious injuries were those in the intestinal tract, although the lungs were also injured. The lesions varied from minimal mucosal hemorrhages to large perforations of the "blowout" type, resembling the tear in concussion of a blown-up paper bag.

The perforations tended to occur where air was pocketed in a more or less fixed position of the gut. Another lesion of importance was the secondary infection and ulceration of many of the nonperforated injuries (hematomas) in the intestinal wall. The possibility of late perforation in this type of lesion must be kept in mind in the clinical management of these patients and in considering the prognosis of immersion blast injury. In two of the autopsies escape of air from the peritoneal cavity could be detected. Obliteration of liver dulness, or x-ray evidence of subdiaphragmatic air or pneumoperitoneum, are important diagnostic signs and should be looked for in the evaluation of immersion blast injuries, both at first and subsequent examinations, because of the possibility of secondary perforation. Fat necrosis was found in the first three autopsies. The lesions were minimal and limited to the omental fat and the fat over the pancreas. No gross or microscopic hemorrhages were found, but marked toxic degeneration of the glandular tissue was present. The area of the pancreas was bathed in fluid exudate. Injury to the lungs was found in every autopsy. The lesions varied from minimal areas of subpleural, inter- and intra-alveolar hemorrhage, with microscopic rupture of the alveolar walls, to massive hemorrhage and collapse of as much as 85 per cent of the air-containing tissue. Hydrothorax or hydropneumothorax was present in all autopsies. A fibrinous pleuritis was found in two of the autopsies, as were patches of peribronchial pneumonia. It is probable that the total injury in both the lungs and the intestines determines, in the first few hours after injury, whether the patient will die shortly or is capable of recovery.

**Clinical Experience**—The results of examination of nineteen critically injured



patients who had survived a sinking at sea and subsequent depth charge explosion revealed that nearly all the patients suffered to some extent from sunburn, conjunctivitis, fatigue, and exposure.<sup>24</sup> In addition, a number had evidence of injury to the chest; in one instance, there was a pneumothorax with fractured ribs, and in the remainder the injury was revealed by the presence of persistent râles. There were several instances of fractures and bruises. There were no ruptured eardrums, no genitourinary injuries, and apparently no patients suffered organic or inorganic injury to the central nervous system from immersion blast.

Since these patients were received thirty-six hours after injury, conservative treatment was decided upon. *Morphine* was given freely, to overcome shock, to relieve pain, and to reduce intestinal activity. No patient was given food or an enema until it could definitely be determined that no intra-abdominal injury was present. *Plasma, dextrose, or saline* was given as indicated by the condition of the patient. In ten instances it was necessary to pass a *Miller-Abbott* or *Wangensteen suction tube*. In four instances oxygen was administered. Of the five deaths, four occurred 7, 27, 30, and 42 hours, respectively, the cause being generalized peritonitis. At no time were these patients in condition for operation. The fifth death occurred at the end of five days, from pooled plasma anaphylaxis. The patient's condition had been deemed satisfactory for operation, and he had been given a supportive amount of plasma. Shock and death immediately ensued.

### Arterial Injuries

**Vasospasm**—This is a protective response to trauma, but if the arterial tree of an extremity becomes, and remains,

constricted, then thrombosis, trophic changes, fibrosis, and lesions resembling Volkmann's ischemic contracture may follow.<sup>25</sup> Of twelve patients with persistent posttraumatic vasospasm in which the arteries were not directly injured, the involved extremities were cold, cyanotic, and often edematous. Vasospasm could be temporarily abolished by paravertebral injections of novocaine (1 per cent). In the more severe cases, preganglionic sympathectomy was performed, with good result. Posttraumatic vasospasm may persist over long periods of time, and may be either segmental or may involve the entire arterial tree of the extremity. If vasospasm is not eliminated by a series of paravertebral "blocks," sympathectomy should be considered.

### Direct Arterial Injuries—*Early*

**Results**—Ligation of the lacerated artery (and usually its concomitant vein) at the time of the initial débridement is usually carried out in most instances. The author's experience with the non-suture anastomosis of blood vessels, suggested by Blakemore and Lord (SEE: *Revision Service Volume, 1945, The Cyclopedia of Medicine, Surgery, and Specialties*), was limited to three patients. Since the anastomosis was undertaken because of laceration of the popliteal artery, it was felt that the result obtained was better than that usually effected without the venous anastomosis. Results on eight patients suggest that early *sympathectomy* in major arterial injuries may help preserve a part, or all, of an extremity.

**Late Results**—There was evidence, in later results of major arterial ligation, of chronic arterial deficiency, characterized by intermittent claudication on walking, "muscle cramps" at rest, weak to absent peripheral pulses, and trophic skin changes, as well as comparative coolness of the extremity. Preliminary

paravertebral injections showed a favorable response, and sympathectomy gave excellent results.

**Traumatic Aneurysms**—These may not be apparent until some days after injury. When present, conservative measures were carried out unless strong indications for early intervention existed.

**Arteriovenous Aneurysms**—Of thirteen patients with traumatic arteriovenous fistula, definite indications for operation were present in six. There were no recurrences, gangrene, secondary amputations, or deaths in any of the patients operated upon, for either aneurysm or arteriovenous fistulas. It is important that the two conditions be differentiated, as both the local and systemic effects are different. It is hoped that further experience with the non-suture anastomosis of Blakemore will lower the incidence of gangrene following sudden trauma to major arteries. This method would seem especially feasible in popliteal artery injuries.

Early operative intervention in traumatic aneurysms was necessary in about 40 per cent of the patients seen. The temporary occlusion of vessels has been accomplished by using a broad cotton tape ligature tied down on a segment of small rubber tubing laid on top of the vessel. When bulldog artery clamps were not available, a screw clamp has been used to obtain partial, or complete, occlusion of the artery after encasing the vessel in a segment of tubing of suitable size. Manual compression by an assistant just proximal to the ligature decreases the tension so that the ligature can be tightened with less danger of rupturing the intima. All vessels are divided and the ends transfixed.

### Facial Wounds

**Primary Closure—Technic**—It is commonly agreed that the only way to

avoid scarring from facial wounds is to suture a vertically cut skin edge into exact edge apposition over a bed of normal subcutaneous tissue, with perfect hemostasis, no tension, and no infection; then to remove the stitches in two or three days. For a satisfactory result, there must also be no distortion of the features.<sup>26</sup> A similar procedure can be used to close the wound at a primary operation. Under local anesthesia, a wound toilet is done, the skin edges are excised and undermined, and hemostasis is secured by hot flavine packs. A subcutaneous tissue layer is then fashioned and closed with catgut, the skin is accurately sutured, and a pressure bandage is applied. The amount of skin excised is no more than would be sacrificed were the wound left to heal and a formal scar correction done. The obvious difference is the danger of infection, and it has been found that forty-eight hours from injury is near the upper limit of safety in the majority of cases. Up to that limit, primary healing in three days may be consistently achieved. The cosmetic standard is generally good, but not quite so good as that of cold scar corrections done under ideal conditions.

In battle injuries, the nasal and buccopharyngeal cavities, maxillary and frontal sinuses, mandible, hyoid, and zygoma are very commonly involved, and experience has shown that these, too, may be closed with consistent success, after a very careful toilet with removal of all loose bone fragments and tissues of uncertain vitality, remembering that any dead tissue left behind is almost sure to suppurate. In cases of mandibular comminution involving tooth sockets, bone suppuration is common, and it is often wise to drain the wound.

The advantages of primary closure are quicker recovery—closure shortens the incapacity period from even the

smallest wounds and the cosmetic result is better; reduction of ward work; and fewer complications—the stage of disfigurement which used to last weeks or months is reduced to a matter of hours.

**Rôle of Penicillin**—In all the major closures and about half the minor ones, *penicillin-sulfathiazole powder*, 0.5 to 1.0 gm., was smeared throughout the wound. The effect of penicillin is not immediately spectacular and cannot be statistically proved, but the following observations were made: Closures of antral and other compound face wounds can be done successfully with or without penicillin. Local penicillin definitely reduces the incidence of stitch infection and cellulitis of the face in the region of a major primary closure. The standard of the successes is raised, but their proportion and the scope of major primary closures are not much affected.

### Delayed Suture

**Rules for Success**—Débridement of wounds at forward units must be thorough. The dressing of a wound *must not* be disturbed during evacuation from forward units to base hospitals, unless the indications for doing so are absolute. The first dressing must be done under aseptic conditions in the operating theater, the optimum time being three to five days after the initial operation. The wound must be closed at once if it looks suitable, bacteriological examination being ignored as a criterion for closure. The patient must be retained in hospital until the sutures are removed.<sup>27</sup>

**Technic**—The patient is not taken to the theater until the day after admission to the base hospital, so that a night's rest is assured. The dressing is then removed with aseptic precautions, and unless contraindications make suture impossible or imprudent, pentothal anesthesia is induced.

Superficial wounds are disturbed as little as possible. Any minor revision, such as removal

of a tag of tissue, is done after the blood clot has been gently removed. The edges of the wound are separated from the underlying structures by blunt dissection and brought into apposition by interrupted sutures. It is important to obtain accurate apposition of the skin edges. In deeper wounds the tract is explored, not only to make sure that no revision is needed but also to prepare the site for the reception of penicillin tubes.

Drainage is rarely employed, except at the angles of the suture line of a major amputation. Buried sutures are avoided as far as possible. With severe fractures, especially those of the femur, there is a tendency to delay suture to the sixth to tenth day.

A certain amount of tension is permitted; but where skin loss is considerable, the edges are brought as close as seems wise, and the operation is completed after five days, by which time it is often possible to secure close apposition. Where skin loss is great a simple flap may be used, or epithelial cover may be provided by immediate patch skin grafts.

After the operation, the limb is put at rest, and as a rule is not disturbed for ten to twelve days, after which stitches are removed in the theater. With deeper wounds, however, or if there is tension after suture, it is increasingly the custom to make an interim inspection in the operating theater after five days. No dressings or inspections are permitted in the wards.

**Contraindications to the Second Stage**—The main contraindications are: (1) Acute inflammation in the wound, or of the tissues around the wound, whether pus be present or not. A "dirty" wound is not necessarily unsuited, for many such wounds show no signs of inflammation, and pyogenic organisms are not more commonly found in them than in wounds which look clean. (2) The presence of gas in the tissues. (3) Excessive loss of skin.

When the wound appears unsuited to immediate closure because of sepsis, it is treated actively with an antiseptic for a few days and then repaired. In many cases progress is controlled by bacteriological examination; but it must be emphasized that suitability for immediate closure (*i. e.*, delayed primary suture)

is determined by naked eye inspection alone.

There are some forms of wound—notably compound fractures of the lower end of the tibia—in which suture is often impossible for mechanical reasons.

**Failures and Their Treatment**—A delayed suture which is less than 50 per cent successful is regarded as a failure. The two common causes of failure are excess of tension at the suture line and sepsis, or both. If failure is complete, a second attempt may be made after preliminary local treatment, usually with *penicillin*. In partial failures, the unhealed area may be covered with patch grafts. In other cases again, it may be best to wait a week or more and perform a “secondary suture.” This term is used to describe the operation required when the time during which delayed primary suture is still possible (usually less than ten days) has elapsed. It is indicated at any time from fourteen to sixteen days onwards. The granulation tissue is removed and the skin edges excised. In effect, the old unhealed wound is replaced by a new one which is immediately closed. Often a flap is needed, and if the wound is large and requires more than the average skill of the general surgeon, the case is transferred to a maxillofacial center. Occasionally failure is due to the retention of unsuspected metal fragments, and, of course, sometimes to sequestra. But no wound is allowed to remain unhealed without good cause.

**Results**—Of the cases treated by delayed suture, 10 per cent were fractures, whereas of the cases treated by secondary suture, 20 per cent were fractures. This is because a higher proportion of fracture cases are unsuited for delayed suture, and because there is a slightly higher proportion of failure of delayed suture in compound fractures,

secondary suture being frequently attempted when delayed suture has failed.

A successful delayed suture looks its best a few days after the stitches are removed. As the weeks pass, the scars, particularly of the larger wounds, often develop a good deal of keloid formation and become red and unsightly. Often the epithelium gives way, especially at the junction of scars, or over the fibrous track resulting from the passage of the missile. Such scars are very troublesome; they may almost indefinitely delay a patient returning to his unit. Wounds of the buttock are the most intractable.

**Rôle of the Forward Surgeon**—Supplementing the report of Edwards<sup>27</sup> on 3435 wounds treated by two-stage operation, Stammers<sup>28</sup> states that stitches and ambulance journeys are incompatible; all soft tissue wounds are best splinted for the journey. When muscle is involved, splinting is essential, and it should include the joint below.

**Procedure in the Forward Area**—First shave a wide surround of skin and wash it with soap and water. Then apply some such antiseptic as *flavine in spirit* or *iodine*. Remove only the pulped or frayed edge of the skin; the skin wound must be extended by incisions long enough to allow retractors to be inserted to the full depth of the wound so that it can be fully inspected. Excise any dirt, fat, or fascia and cut off any tags of fascia. Remove all muscle that does not bleed or does not contract when cut (imperfect removal of devitalized muscle carries the risk of gas gangrene, and in any case leads to sepsis and hence to a wound unfit for early suture). Remove any pieces of bone that have no periosteal attachment. Remove any indriven clothing, equipment, or dirt, and any fragment of metal that is readily accessible. Lay open all nooks and crannies in which pockets of pus may collect. Make generous incisions into the deep fascia, transversely as well as longitudinally, as a prophylactic decompressive measure.

At the end of the operation a good frosting of *penicillin-sulfonamide powder* is applied, and during operation many surgeons pour into the wound 1/1000 *acraflavine* or *proflavine*.

A dressing of *sulfanilamide-paraffin gauze* is applied, but no packing and no stitches are permitted.

One need not be afraid of making a long incision: it can be closed at the base, and indeed it is easier to suture than a circular hole. Adequate incision is particularly important where there is a deep and extensive muscle wound lying beneath a small wound of entry. Where a through-and-through wound is superficial it is best to join the two together, but where it transfixes deeply—as through the quadriceps or deep to a vascular bundle—each wound should be treated separately as above.

For major muscle wounds (buttock, thigh, calf, axillary folds) a three-day course of *penicillin*, either *intramuscularly* or by *glucose-saline drip*, is given. The dose is 15,000 units three-hourly.

An essential part of treatment is *adequate splinting*. Quite apart from fractures, every wound involving muscle should be splinted, the best form being a plaster back-slab or a light cast; it should include the joint below, for otherwise the patient travels in pain and the wound is pulled on by the irregular movements of the ambulance. Experience shows that Cramer wire is too springy to give comfort during travel over rough roads.

**Two-stage Operation**—In further elaboration on the British Army's technic in this treatment, Capper<sup>29</sup> states that for success two factors are essential: (1) Early adequate planned decompression of the wound at the initial operation forward, and (2) facilities for early transportation of the wounded man to a center where definitive surgery is possible and where he can be retained for ten days or more. The benefit of early operation outweighs the advantage of any preparation beyond twenty-four hours' painless rest and adequate fluid intake.

**Some Points in Technic—Local Chemotherapy**—According to the type of wound encountered, it is treated with a powder or with *penicillin solution*. The powder was either 1 per cent *proflavine in sulfathiazole* or *calcium penicillin*; they appeared to be of equal value. *Sodium penicillin solution* (250 units per cc.) has been used where it was impossible to get adequate débridement in a long

tracking wound through muscle groups or near vital structures, or where it was impossible to avoid dead space; it is introduced through fine rubber tubes. Adequate drainage is important to get rid of the gram-negative pus that collects in these spaces, and this is best removed by aspiration of the tubes twice a day before the introduction of the fresh solution.

**Systemic Chemotherapy**—A course of *sulfathiazole* by mouth after operation seems to be of definite value.

**Repair**—Fine sutures of silkworm gut closely placed give the best results, and where the skin edges cannot be straightened, vertical mattress sutures or a pulley-stitch are of special value. Deep tension sutures over buttons may be used with advantage, especially in buttock wounds, where maintenance of apposition of the deep tissues is difficult. Buried sutures are for the most part unnecessary and better avoided.

Dead space is unavoidable in many of the wounds. If it is deeply situated, the best course is to introduce a *penicillin tube with dependent drainage*. By the seventh day, when the tube is removed, most of the space will have been obliterated by the fast-growing hemorrhagic granulation tissue that forms in the presence of penicillin. The hole for the drainage tube can then be sutured if necessary. With superficial dead space, it is best either to rotate a skin flap to fall into the underlying hollow, or to suture the skin edges to the shelving walls of the gap and cover the intervening space with a split-skin graft.

**Immobilization**—The importance of a firm pressure bandage, of absolute fixation of the part in the plaster, and of elevation, cannot be exaggerated.

**Contraindications**—The most common are:

**Established Infection**—Such a wound must be further decompressed and the part must be splinted and elevated for five days, after which secondary suture may or may not be possible.

**Incomplete Wound Excision**—These cases need further excision. Suture will probably be possible in five days.

**Involvement of a Blood Vessel**—In a wound where a large blood vessel may have been damaged, and where it is impossible to ensure absence of sepsis, suture may be the prelude to secondary

hemorrhage; secondary hemorrhage has been rare in such wounds when allowed to drain.

*Joints*—Where a joint is open in the wound it is best to attempt closure of the capsule or its adjacent structures and to wait five days before closing the overlying skin.

In conclusion, Brown<sup>30</sup> states that *penicillin* as a local bacteriostatic has so revolutionized the delayed closure of soft-tissue wounds that the two-stage method has become firmly established as the best form of therapy. Success depends first and foremost on adequate primary surgery. No bacteriostatic, however effective, must be allowed to replace thorough wound excision, and the results of the two-stage treatment are a tribute to the work of surgeons in the forward area.

These results are corroborated by Hendry, Gledhill, and Price,<sup>31</sup> who found that the two-stage method of suture with routine penicillin gives a high proportion of wounds healed in fourteen days. Local insufflation of a *sulfonamide powder* or *penicillin powder* at the time of the primary operation improves results.

Further results in open battle-casualty fractures reported by these same authors showed that within six weeks of wounding, 75 per cent were closed when treated by *local application of penicillin supplemented by a short course of parenteral injections* of the drug. When complete suture could be performed, 87 per cent were closed in six weeks. Local instillation of penicillin to the fracture site is the method of choice, being both effective and economical. The transformation from open to closed fractures promotes early union and speedy return of function.

These conclusions were further supported by Atkins and Holden,<sup>32</sup> who

state that success depends on *careful surgery, hemostasis, avoidance of "tentage," correct dosage of penicillin, application of firm pressure dressings, and adequate immobilization* after the operation.

Bhatia<sup>33</sup> also states that suture of wounds has reduced the average period of stay in hospital. It minimizes frequent painful dressings and discomfort to the patient. It also reduces the incidence of chronic sepsis. The patients visibly improve. They feel better, develop hearty appetites, and look cheerful.

### Colon and Rectal Injuries

#### Management in the Forward Areas

—Initial surgery of thirty-nine injuries of the colon and rectum was performed by a general surgical team of an auxiliary surgical group. Most of the injuries were caused by fragments. Twenty-nine patients were operated upon within twelve hours of injury; five within six hours. A short time interval can contribute toward an increased mortality, because more of the severely wounded come to surgery. The average time interval was fifteen hours. The contribution of shock toward an increased mortality was exemplified by five deaths, in spite of vigorous replacement therapy, out of eight patients admitted in severe shock. The second part of the duodenum was injured in two of four injuries of the hepatic flexure. Peritoneal contamination and early infection responded gratifyingly to forward surgery and its adjuncts, *sulfonamides* and *penicillin*, for only twelve patients exhibited objective signs of peritonitis. Eight patients sustaining injuries of the colon or rectum alone were treated successfully. Thirteen colon injuries complicated by severe concomitant wounds died—a mortality rate of 33.3 per cent. Severe shock, secondary to injuries of the colon complicated by

concomitant wounds, was the dominant cause of death. Next to shock, sepsis was the leading cause of death.<sup>34</sup>

**Injuries of the Extraperitoneal Rectum**—According to Croce, Johnson, and Wiper,<sup>35</sup> perforation of the intraperitoneal portion of the rectum results in fecal contamination of the cellular tissue of the intraperitoneal space. This space communicates with the retroperitoneal space posteriorly over the sacrum and may, thus, result in fulminating and widespread retroperitoneal sepsis. Even if the perforation cannot be located, but there is a presumptive evidence of its presence or potential development from contusion or infarct of the rectum as judged from the course of the missile and the presence of a large hematoma in the intraperitoneal space, an effective sigmoid colostomy should be established at once. A sigmoid colostomy alone will not prevent infection of the intraperitoneal space, although the infection is likely to be less widespread and fulminating once contact with the normal intraluminal pressure and gross contamination of normally functioning bowel is severed. In addition, the intraperitoneal perirectal space must be saucerized by *coccygectomy* and loosely packed. Mere saucerization of the perirectal space, while lifesaving and prophylactic against spreading retroperitoneal sepsis, is not, however, a completely ideal treatment. Unless the perforation is located and closed, a persistent fistula may develop.

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## THE ABDOMEN

**Abdominal Injuries at the Base Hospital**—In fifty-five soldiers wounded during the campaign in Normandy and the Low Countries, a review was made of the treatment and complications after

they had arrived at civilian base hospitals in the United Kingdom.<sup>36</sup> They were a selected group, in view of the fact that they were considered fit to be evacuated by air, and no conclusions can be drawn from them regarding methods of primary treatment or the mortality rate. Very few of them caused anxiety on arrival, in spite of extensive injuries, and this is attributed to the liberal employment of *blood, plasma, and saline infusions*, to *routine gastric suction*, to *systemic penicillin therapy* in every case, and to the policy of *exteriorizing or excluding all wounds* of the large intestine. Many of these patients had other wounds apart from their abdominal injuries, but in almost every case it was the wound in the belly which dominated the clinical picture.

On arrival of a convoy, patients who have had wounds of the abdomen or of the buttock should be examined as soon as they are settled in bed, and any untoward symptoms, such as pain, vomiting, or hematuria, must be accounted for, and raising of the pulse rate or temperature explained. Pain or fever may be due to a residual abscess in the abdomen, or to an infected wound which is draining inadequately. A full course of *systemic penicillin therapy* will probably have been administered before arrival at the base, but if this is not the case, or if there are any signs of spreading inflammation, systemic penicillin should be instituted at once, in the latter instance without waiting to determine the nature of the infecting organism. A further course of penicillin should be instituted shortly before undertaking any operation on an infected abdominal wound, provided the infecting organism is penicillin-sensitive. The onset of vomiting and colicky pain should arouse the suspicion of acute intestinal obstruction by a band, and if examination supports

this diagnosis *laparotomy* should be undertaken at once.

With exception of fistulas into the upper part of the small intestine, there is no hurry about the closure of colostomies and other fecal fistulas, and the patient's general condition should be adequately restored first. Most small intestinal fistulas will close spontaneously, but not those of the colon or rectum. As a general rule, such fistulas are not finally closed until any other wounds which the patient has received are healed, and often a series of operations is necessary to close them. However, when fecal contamination of a wound is a cause of continued suppuration, with resulting persistent toxemia, steps must be taken to divert the flow of feces, either by a *short circuit operation* or by a proximal *colostomy*. Scrupulously careful technic is essential if the operations for closure of fecal fistulas are to be uniformly successful, while scarring and adhesions may add to the difficulties.

Suprapubic bladder fistulas usually close spontaneously, but before removing the tube it is essential to be sure that the wounds in the bladder are healed and that there is no obstruction to the urethra; if the bladder wounds have not been sutured at the primary operation, they may require repair later. Abdominothoracic wounds, after their early treatment, present no peculiar problems, the injury to each cavity requiring attention as a separate entity, provided no communication between the cavities persists.

Many of these patients have, when healed, large scars in the abdominal wall, which may be a source of weakness, but a period of rehabilitation does much to restore their strength and their self-confidence.

Undoubtedly other complications will arise which were not encountered in this

small series. Though their treatment is not completed, there is every reason to suppose that, with the exception of one man who died as a result of another wound, they will all survive, and will be left with little or no permanent incapacity as a result of their abdominal injuries.

**Combined Injuries of the Thorax and Abdomen** — Eighty-three patients having injury to both the thorax and abdomen were admitted to an evacuation hospital in a six-month period.<sup>37</sup> These combined injuries accounted for about one fourth of all penetrating or perforating wounds of the chest and abdomen. Chest and abdominal wounds each give rise to problems in management; when both are present, difficulties may be doubled and certain problems peculiar to combined injuries are added. Furthermore, more than half of these patients had associated injuries of varying severity. That left-sided wounds are more serious than right-sided ones was evidenced not only by the smaller number of the former who lived to reach the hospital, but also by their higher hospital mortality. Twelve of the thirty-three patients with left-sided injuries died, while eight of the forty-eight with injuries on the right side succumbed. Both patients with chest injury on one side and abdominal injury on the other died. On the right side the liver offers an important barrier to missiles and perforation of the intestine is less common than on the left.

From the diagnostic standpoint, it is most important first to keep in mind the frequency with which both cavities are involved in missile wounds of one or the other. While the diagnosis may be clinically obvious from the signs and symptoms and from the location of the wounds, roentgenologic search for all missiles and reconstruction of their course will reveal the diagnosis when the clinical findings



are equivocal. Experience in the correlation of the findings at operation with the roentgenologic data aids in predicting organ involvement and in planning the surgical approach.

Every attempt must be made to bring even the most seriously injured patients to surgery since the arrest of hemorrhage and the correction of respiratory physiology may offer the best treatment for their shock. Overcaution in delaying operation until shock therapy has produced satisfactory pulse and blood pressure readings may be fatal in these cases. Patients who require *thoracotomy* because of a large hemothorax or sucking chest wound usually improve during surgery. Patients with severe abdominal injury also frequently improve during operation, but to a lesser extent. Excluding three cases in which no surgery was indicated, seventy of the eighty patients were operated upon and ten died without operation, making the operability rate 88 per cent. Although operative attempts to save desperately injured casualties may prove futile, the operative mortality rate should be disregarded in the effort to save at least some of the patients.

The proper course of treatment of combined injuries varies from no surgery at all to the most extensive combined thoracic and abdominal operations. Conservative management has an important place in the treatment of right-sided injuries involving small penetrating or perforating wounds of the liver or kidney without serious intrathoracic damage. Occasionally nothing need be done; in others, *débridement and exploration of the wound, closure of the opening* in the pleura, and *aspiration of the hemothorax* are indicated. These procedures along with *suture of the kidney* usually suffice for thoracoretroperitoneal wounds as well. Thoracotomy

was performed forty-two times, but in only five instances was a separate celiotomy incision necessary, and in seven cases exploration and repair of the involved portions of the thorax and abdomen were carried out through the same incision. Transdiaphragmatic procedures on the liver, spleen, and stomach are technically easier if performed at celiotomy. On the other hand, celiotomy alone should be performed if intrathoracic damage is minimal. If both thoracotomy and celiotomy are necessary, the one which will do the patient the most immediate good should be undertaken first. Unless intra-abdominal bleeding is present, thoracotomy should take precedence, since the correction of pathologic physiology due to open pneumothorax or a large hemothorax greatly improves the patient's general condition and increases his ability to withstand other necessary surgery. See War Injuries of the Chest, p. 879.)

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## GAS GANGRENE

It cannot be too strongly emphasized that the clinical picture of gas gangrene still conforms accurately with those vivid descriptions that have come to us from the surgeons of World War I. Indeed, where there is any reasonable doubt about the correctness of the diagnosis the condition is almost certainly *not* gas gangrene. The criteria of diagnosis—the local pain and swelling, the rapidly increasing toxemia, the peculiar mental changes—are too well known to need further discussion; but in the final resort the diagnosis must rest on the local reaction and the answer to the crucial question: Is dead muscle present and is it certain that this muscle has not died from vascular damage or from direct trauma?<sup>38</sup>

*Rapid evacuation* of the wounded, *early and radical surgery*, *penicillin* and *sulfonamides*, prophylactically and therapeutically, *gas gangrene antitoxin*—all are important in treatment. Yet experienced surgeons agree that the most important single factor in the control and cure of gas gangrene is still good surgery; thorough removal of dead and devitalized tissue as soon as possible after wounding, and *radical excision of infected tissue* when gas gangrene is apparent or expected.<sup>39</sup> These facts are discussed more widely below.

### Antitoxin and Chemotherapy

**Toxin and Antitoxin**—The *Clostridium welchii*, according to MacLennan and Macfarlane,<sup>40</sup> elaborates a powerful and complex exotoxin, the action of which is believed to be responsible not only for the rapid spread of the disease but by its wider dissemination for the profound toxemia and high fatality. The fact that the administration of antitoxin has been shown to have therapeutic value lends support to such a view. However, in work with this antitoxin, these authors have come to the conclusion that as diagnostic procedures in early gas gangrene neither the lecithovitellin nor the hyaluronidase tests have proved satisfactory. This leads to the possibility that the profound toxemia of gas gangrene is not due solely or even primarily to alpha toxin. In further research along these lines, these same authors<sup>41</sup> have seen a possible relationship between the toxemia of gas gangrene and that seen in other forms of shock, and have indicated lines for future research.

In a study made by Hall,<sup>42</sup> it seems that whenever it is possible to undertake adequate surgery promptly, anerobic infections may be prevented by this means alone, without recourse to the

administration of either *prophylactic serums* or *prophylactic drugs*. However, the prophylactic use of either serums or drugs, or both together, may serve a valuable purpose in making both early and delayed surgery more secure, or in permitting primary closure of a wound which would otherwise be left open. But they are never to be regarded as a substitute for adequate surgery.

The treatment of infected wounds under catastrophic conditions, as in war, must be based upon the assumption that prompt surgery is generally impossible. Under these conditions, the injection of polyvalent, preferably pentavalent, *gas gangrene antitoxin* and *tetanus antitoxin* assumes a major prophylactic rôle. It is necessary to guard against anaphylactic shock.

**Chemotherapy — Sulfonamide drugs** and *penicillin* may serve a similar prophylactic rôle. One can only point out that the conditions under which most civilian wounds are treated are so different from those under which war wounds are treated that it is scarcely possible to reason from one to the other.

According to Sachs,<sup>43</sup> clinical results before and since sulfonamide therapy came into common use do not substantiate the effectiveness of these drugs as suggested by experimental work. Of the sulfonamides, *sulfathiazole* and *sulfadiazine* are most effective. However, local use of the drugs has failed to lower the incidence of infection.

In spite of poor experimental results with *irradiation*, the clinical ones are good. The protective agent produced by this treatment is probably a proteolytic enzyme which is released when the highly sensitive leukocyte is subjected to irradiation. Most inflammations will respond to irradiation within from thirty-six to forty-eight hours. Surgery still remains the choice therapeutic agent.

However, results obtained recently with irradiation and chemotherapy point to better results in the future provided close cooperation is maintained between the surgeon, radiologist, and bacteriologist.

**Penicillin**—Of seventy-six cases ill with systemic reaction and clostridial infection, all were treated with **systemic penicillin**, 20,000 units intramuscularly every three hours.<sup>44</sup> The average dosage in nine severe cases was 1,950,000 and forty-one moderate cases 1,700,000 units. In the majority of patients, 30,000 to 50,000 units of **antigas gangrene serum** was given before operation. Possible significant features in the biochemical findings were low blood cholesterol and high urine creatine levels. Acidosis did not appear to be greater in this group than in other wounded men. There were two deaths.

### General Treatment

Cases developing severe clostridial toxemia early (twelve to twenty-four hours) occur in forward areas in men whose resistance to infection may have been lowered by exposure and the stress of battle. Major arterial lesions are often present. In a series of thirty-three cases,<sup>45</sup> the disease was recognized after a longer interval (four to five days) and major vascular injuries were few (four cases). The general resistance of the patients should have been better, and the virulence of the infection may well have been modified by the usual prophylactic measures (**serum**, **sulfonamides**, or **penicillin**). So that no chance of benefit should be lost, all the patients had a combined form of therapy—**surgery**, **penicillin** (local and parenteral), **blood transfusion**, **antiserum**, and **sulfathiazole**. Response to treatment was uniformly satisfactory; as a rule, there was little cause for concern once the routine

had been instituted. Since the only addition to treatment was the intensive use of penicillin, some of the credit for the results obtained must be attributed to this drug; but its mode of action is by no means clear.

Staehle and Ruehlman<sup>46</sup> report thirteen cases of gas bacillus infection treated with large doses of **sulfadiazine** and **gas bacillus antitoxin**, together with repeated transfusions and supportive treatment. All survived. Amputations were done on three cases. Apparently the combination of sulfadiazine and gas antitoxin, together with adequate surgery, was responsible for the remarkable absence of deaths. Another large factor in these good results was that all patients were young, robust, healthy males.

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## TRANSFUSION

### Wartime Transfusion Work—

Transfusion work in war is essentially of an emergency nature. All possible short cuts to eliminate error and lengthy procedures are necessarily employed. On the battlefield, for instance, the only blood used is that obtained from the universal donor; homologous transfusion is not even contemplated, at least not in forward areas. In war, the main requirement is restoration of blood volume and the treatment of the simple anemia of hemorrhage. For this, stored blood is eminently suitable. In war, the commonest recipient is the fit young soldier whose cardiac musculature was in perfect order before his wounding. To him, large volumes need to be and can be administered at a fast rate without fear of overloading the circulation or producing pulmonary edema). Indeed, almost the only contraindication to enthusiastic transfusion in the wounded are injuries to the brain and central nerv-

ous system (in which little response is obtained), damage to the lung by blast, irritant gases, or steam (which often causes pulmonary edema), thoracic wounds where the circulation is mechanically impeded, and the onset of the fat embolism which may follow bone damage. In war one takes many a chance one cannot afford in peace.<sup>47</sup>

General experience has shown that 10 to 15 per cent of wounded men require to be transfused, and that the average casualty for whom transfusion is necessary requires about four pints of protein fluid.

## ACTINOMYCOSIS

In six cases of actinomycotic infection, only two had had a diagnosis of actinomycosis made before admission to the hospital.<sup>48</sup> These cases illustrate the fact that *penicillin* is an effective agent in combatting this disease. The response of one case was nothing short of miraculous. Several of these patients were treated with repeated intravenous injections of penicillin; this method has been discarded, as the intramuscular route is undoubtedly superior. Surgical excision of scar and underlying fibrous and granulation tissue was undertaken in two cases. This step is a good adjunct to penicillin therapy where there is marked overgrowth of fibrous tissue. Both cases healed *per primam*. It is evident because of the nature of the disease process that penicillin must be administered for an adequate period of time. Experience shows that it usually requires six to eight weeks.

There is little doubt that the *sulfonamides* are effective against this disease; it might well be that a combination of the two drugs could be employed to advantage. However, penicillin seems to be the most effective single agent.

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## DISEASES OF THE TEETH AND MOUTH

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### Introduction

During the past year the health service aspects of dentistry have received wider recognition, both by the members of the medical and dental profession and also the laity. There has been an increasing interest in long-range caries-control experiments in which predetermined amounts of fluorine are added to the community water supply. Caries control by the topical application of fluoride salts has received further consideration and the accumulated evidence suggests that the time is rapidly approaching when the dentist can offer a reasonably satisfactory caries-preventive treatment for the younger patient.

The numerous reports concerning the use of penicillin in the treatment of diseases of the oral mucosa have furnished us with a better understanding of the indications and contraindications for the use of this antibiotic agent. *Penicillin* has been demonstrated to be of definite value in the treatment of many diseases of the oral structures, but in others this form of therapy has shown no advantages over agents which have long been in use.

The epidemiology of fusospirochetal infections in the military services, has been extensively studied by Dean and Singleton of the U. S. P. H. S. Their findings form a distinct contribution to this phase of the subject. The indications for topical and systemic penicillin therapy in the

treatment of fusospirochetal gingivitis and stomatitis have been clarified.

The oral focal infection question has received considerable attention. Its significance has been critically and conservatively evaluated and its causative or aggravating rôle in many extraoral diseases is being better appreciated.

### Dental Caries

There was increased lay and professional interest in the fluorine-dental public health problem during the past year. The present status of dental caries control was given in a symposium which was sponsored by the New York Institute of Clinical Oral Pathology.<sup>1</sup>

Dean of the U. S. P. H. S. reviewed the extensive epidemiologic studies which have been made by this service. There is definite evidence that a fluorine concentration in the drinking water of one part per million, or slightly higher, has a marked effect on the caries process. This is manifested by about six times the number of caries-free individuals; a 60 per cent lower dental caries experience rate and about 75 per cent decrease in the first permanent molar loss as compared to similar findings in an area of fluorine-free drinking water. Dean, however, feels that much more investigative work will be required before a recommendation can be made in respect to a general application of the addition of fluorine in accurately con-

trolled amounts to the commercial water supply.

It is of interest in relation to the fluorine-dental health problem that the chemical content of carious as compared to noncarious teeth shows a significant difference. The fluorine content of the enamel of carious teeth is only 62 per cent of that of sound teeth. Statistical analysis has shown that there is much less than one chance in 5,000,000 that the higher amount of fluorine in the enamel of the sound teeth in comparison to that of carious teeth is accidental. There was little difference in the fluorine content of the dentine of the sound and carious teeth. It is believed that the higher fluorine content of the enamel of sound teeth, compared to that of carious teeth, gives to the enamel properties which are associated with an increased resistance to caries.

The caries-preventive effect of the topical application of fluoride-containing solutions has received further study. This phase of the problem is of special importance to the population groups residing in rural areas, approximately one third of the population, and in individuals whose adult dentition has already developed and erupted for some years. There is definite evidence that the fluorine content of erupted teeth (enamel) can be increased by the topical application of fluoride-containing solutions, especially in the recently erupted tooth. Repeated applications following a dental prophylaxis are required. The reduction of new cavities is from 40 to 60 per cent in the treated teeth. Bibby has determined the effect of incorporating fluorides in the cleaning mixtures used by dental hygienists in ordinary dental prophylaxes. The usual treatment was not modified except by incorporating in the peroxide-pumice mixture sufficient 4 per cent NaF solution to give a 1 per cent

concentration of fluoride in the final mixture. He observed approximately a 25 per cent and 43 per cent reduction in dental decay as the result of two or three cleanings per year.

Ast described in detail the controlled studies being made at Newburg, New York, in conjunction with the fluoridization of the water supply of this city to a concentration of approximately one part per million (present concentration 0.05 to 0.15 p.p.m.) In addition to the detailed dental studies, regular and periodic pediatric examinations will be made to determine the effects, if any, of fluorine on the growth and development of the children. These studies are being made on 500 children from birth to twelve years of age. X-ray studies of the bones and centers of ossification and laboratory tests including blood and urine analyses will supplement the physical examinations.

One of the presumed hazards of the addition of fluorine to the public water supplies is the possible toxic cumulative effect of this element. McClure and Kinser<sup>2</sup> found that where the domestic waters were free of fluorine, the fluorine present in the urine averaged 0.3 to 0.5 part per million. The fluorine in the urine was proportional to the fluorine content of the drinking water through the range of 0.5 to 5.1 parts of fluorine, per million in the domestic water. An efficient elimination of fluorine appeared to be a characteristic of persons residing in certain areas of the United States where the drinking water contains 0.5 to 5.0 parts of fluorine per million. The metabolism of fluorine under these conditions seems to be a normal function of the human body and is characterized, at least in the adult, by a condition approaching a metabolic equilibrium.

Preliminary studies made by Retarski *et al.*<sup>3</sup> showed that when extracted teeth

were immersed in a common "cola" beverage that decalcification of the enamel surface could be observed grossly after two days' immersion.

A series of rat and puppy experiments was undertaken in which a specified amount of the "cola" beverage or a sugar-phosphoric acid solution of the same strength was consumed. The  $pH$  of the "cola" beverage was 2.6. Similar solutions to which sodium fluoride in amounts varying from 1 p.p.m. to 20 p.p.m. were added were also studied in respect to their tooth-decalcifying properties.

Severe destruction of the enamel on the molars of white rats was produced by allowing the animals to drink the "cola" beverage for periods of five days or more. With prepared solutions of the same sucrose and phosphoric acid concentration and the same  $pH$  as the commercial product, similar results were observed. Preliminary observations on six puppies showed that the consumption of acid drinks also produced gross and microscopic changes on the deciduous teeth.

The inclusion of 1 to 20 p.p.m. of fluorine as sodium fluoride in the acid beverage decreased but did not prevent completely the destruction of the enamel in the majority of the rats studied. Within the limits tested, no apparent differences were observed in the protective action of different levels of fluorine.

The presence of sucrose in the acid drink aggravated the effect of the acid. The molars of rats receiving a 10 per cent sucrose-phosphoric acid solution were much more affected than those of comparable group receiving an equal amount of saccharin-phosphoric acid solution of the same sweetness, viscosity and acidity.

It is believed that fermentable carbohydrates are essential for the initiation

of the caries process. The caries-producing effect of the various carbohydrates is roughly related to the rapidity of their breakdown. Grubb<sup>4</sup> found that sorbitol, a sugar alcohol, was fermented by the usual oral flora much more slowly than either dextrose or sucrose. He suggested that sorbitol might be substituted for sucrose or dextrose in the sweetening of foods, beverages, and confections. In view of the slow fermentation of this sugar, it might be useful in the prevention or control of dental caries.

Attempts are still being made to devise a simple test for caries susceptibility which will be practical for use in the dental office. Several investigators have reported a high positive correlation between the salivary amylase, which is relatively easy to determine, and dental caries. Others have not found this to be true. Bergheim and Barnfield<sup>5</sup> studied the salivary amylase level and the amount of dental decay in 250 medical and dental students. Salivary amylase was determined by the standard method. No correlation was found between the salivary amylase and the prevalence of open carious lesions.

While calcium, phosphorus, and vitamin D are essential for the developing teeth, their effect in above-optimal or sub-minimal quantities has not been shown to affect the tooth to any serious extent. Smith and Light<sup>6</sup> came to the conclusion that acute disturbances of the skeletal structure may occur with slight change in the dental structures. Although the acute calcium deficiency in the diet of young dogs produced drastic effects on the skeletal structure, including spontaneous fractures and widened uncalcified cartilaginous zones, there was little effect on the structure of the teeth and the alveolar process. Severe enamel hypoplasia or other structural modifications were not observed. The teeth were all

tightly fixed in their alveoli and the radiographs showed normal alveolar structure.

### Fusospirochetal Organisms in Third Molar Infections

The incidence of the fusiform bacillus and Vincent's spirochete in infections about partially erupted third molars was studied by Lenburg.<sup>7</sup> The bacterial smears were considered negative when spirochetes and fusiform bacilli were not predominant in the field. A total of 100 cases was studied. Four of the thirty-one patients with acute symptoms associated with a partially erupted third molar had negative smears for fusospirochetal infection while only four of the sixty-five patients with nonacute symptoms had positive smear findings for this disease. If the smear indicates a predominance of Vincent's organisms, the area should be treated as for ulcerative gingivitis. The treatment of these areas included the application of 3 per cent  $H_2O_2$  on pellets in the office and a mouthwash of 1½ per cent  $H_2O_2$  at home every two hours. Frequent irrigation and removal of débris from beneath the operculum are beneficial. For permanent results the occluding surface of the tooth should be removed, either by extraction or grinding the occluding surface of the offending tooth of the opposing jaw.

### Vincent's Infection

Dean and Singleton<sup>8</sup> contributed significantly to our understanding of the epidemiology of Vincent's infection. The dental admission records of approximately 75,000 men in the Maritime training program, the U. S. P. H. S., the U. S. N., and the Coast Guard were available for study. The records of all new admissions for Vincent's infection, questionable Vincent's infection, or gin-

givitis other than Vincent's infection were transferred to punch cards for subsequent analysis. A total of 3385 such cases was available for statistical study.

During 1943 there were 1578 cases of Vincent's infection admitted to the clinic, 311 cases of questionable Vincent's infection, and 1496 individuals with gingivitis other than Vincent's. Analysis of these data revealed that the epidemiology of Vincent's infection is still confusing and largely undefined. The annual admission rate for this disease for 1943 in the U. S. C. G. was 73.1 per 1000 strength; for the U. S. Maritime Training Service, 94.9 per 1000 strength.

Vincent's disease is predominantly a dental problem. In 1943, 1578 cases of Vincent's infection were admitted to the dental clinic in contrast to 47 cases of Vincent's angina which were admitted to the hospital. From the treatment standpoint, it was found that the removal of as much as possible of the irritants such as supragingival and subgingival calculus, soft débris, etc., at the first sitting, and the use of a bland medication in conjunction with full patient cooperation in attaining and maintaining a high level of oral hygiene were effective in restoring gingival health. The medicament used consisted of 1 gm. *brilliant green*, 1 gm. *crystal violet*, and 50 per cent *alcohol* q s. 100 ml. Cox<sup>9</sup> found that intramuscular *bismuth* injections shortened the duration of the disease and reduced the incidence of recurrences.

The reporting of Vincent's infection by state health departments is variable. Sebelius<sup>10</sup> obtained the following information from twenty of the twenty-two state health departments where Vincent's infection is a reportable disease. In eleven states, Vincent's angina is re-



ported as Vincent's infection. Only six of the twenty health departments have a description of the disease. All replies indicated that the present reporting does not give a true picture of the prevalence of this disease. Physicians only report Vincent's infection in six of the states. The most common method of diagnosis was thought to be both laboratory and clinical. Sebelius felt that if Vincent's infection is to remain a reportable disease, and the data received are to be considered comparable, a better understanding of the entire clinical picture will

250 to 500 units of penicillin per cubic centimeter four times daily. Daily smears were obtained and treatment was continued until the smears were negative for the fusospirochetal organisms. The higher concentrations were most effective. The comparative therapeutic results as obtained with *sodium perborate* and *hydrogen peroxide*, *chromic acid* and *silver nitrate*, and *oxophenarsine hydrochloride* with *sulfadiazine* as lozenges and with local penicillin as shown in Fig. No. 1. Penicillin was the most effective therapeutic agent.

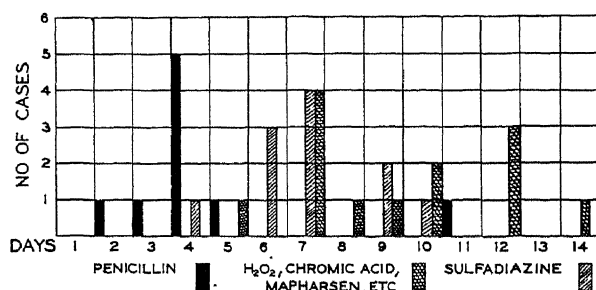


Fig. 1—Comparative therapeutic effect in Vincent's infection of (1) hydrogen peroxide, chromic acid, oxophenarsine hydrochloride and so on and (3) penicillin. The ordinate indicates the number of cases. The abscissa indicates the days on which smears became negative for Vincent's organisms (Shallenberger, P. L., Denny, E. R. and Pyle, H. D.: J. A. M. A. 128: 706 (July 7) 1945.)

be necessary as well as the epidemiologic and bacteriologic aspects of the disease.

**Treatment with Penicillin**—Shallenberger, Denny, and Pyle<sup>11</sup> found that the clinical and bacteriologic response in cases of fusospirochetal angina treated with local penicillin therapy were striking. There was improvement in the appearance of the ulcerations in twenty-four to forty-eight hours and a relatively rapid subsidence of the symptoms. Pain was rapidly relieved in those patients who were suffering severely. The grayish membrane would often start receding in from three to five days from the beginning of the treatment.

The involved tissues were swabbed with penicillin in a concentration of from

Schwartz<sup>12</sup> treated fourteen cases of Vincent's angina with *penicillin*. Clinically the local lesions on the tonsil or the pharynx had the following features in varying severity and combination: Hyperemia, ulceration, exudation (pseudomembrane), bleeding, a characteristic odor, submaxillary lymphadenopathy, edema, and a mild gingivitis. One patient had a temperature of 101.2° F. (oral). The others either had a slight fever (99° to 100° F.) or were afebrile. Symptoms in every case were pronounced. Diagnosis was established by positive clinical and laboratory findings. No smear was considered positive unless there was unequivocal profusion of characteristic spirochetes and fusiform ba-

cilli. The differential leukocyte count revealed no abnormal cells.

Penicillin was injected intramuscularly in each case. The ease with which locally applied penicillin penetrates to the depths of the exudate-covered ulcer is unknown. Furthermore it has been shown that parenterally injected penicillin is secreted in the saliva. Thus, when the intramuscular route is employed, the deep portions of the local lesion will be constantly attacked by penicillin conveyed in the blood stream while the superficial portions will be continually bathed by the penicillin present in the saliva.

The first patients were treated with a total of 200,000 units of the sodium salt administered in 20,000-unit doses intramuscularly every three hours. The response was so satisfactory that all subsequent cases, with three exceptions, had the dosage reduced to 100,000 units administered in 20,000-unit doses every three hours. The smaller doses were found to be only temporarily effective in patients with Vincent's gingivitis.

The hematologic findings in patients with fusospirochetal stomatitis were studied by Burket.<sup>13</sup> Data obtained from 110 cases of fusospirochetal stomatitis were analyzed and compared with similar studies made on a like number of patients with periodontal disease.

There were no characteristic alterations in the blood count findings in the 110 patients with fusospirochetal stomatitis which would aid in the diagnosis of this disease. The blood count may be very useful, however, in ruling out certain of the blood dyscrasias which may produce oral lesions which can be confused with those due to the fusospirochetal organisms.

The total leukocyte counts ranged from 2900 to 16,000 cells per cmm. with 78 per cent of the counts falling

within the range from 5000 to 10,000 which is accepted by Wintrobe to be the normal range. The percentage contribution of the neutrophils and lymphocytes to the total leukocyte count was essentially normal. When the absolute cell counts, neutrophils, and lymphocytes were compared with the normal range of values, there was no indication of a consistent relative lymphocytosis in this disease.

The hematologic findings of 110 cases of periodontal disease were compared with those obtained from the patients with fusospirochetal stomatitis. The range of the leukocyte counts in both groups and the relative distribution of the counts were similar.

Rosenthal<sup>14</sup> found that *penicillin* solutions topically applied were of value in the treatment of acute streptococcal and fusospirochetal infections of the mouth.

### Chronic Desquamative Gingivitis

Ziskin and Zegarelli<sup>15</sup> reported their observations on twelve cases of chronic desquamative gingivitis which were characterized by red, raw, painful hemorrhagic gums. Anti-Vincent's or conservative *periodontal treatment* had been administered. *Liver* and *vitamin B* and *C therapy* as well as *radiation therapy* and *autovaccines* had been used. These forms of treatment proved unsuccessful.

The group of patients studied included ten women and two men. Based on earlier experimental studies which showed that *estrogen therapy* stimulated epithelization as well as connective tissue formation, these agents were tried clinically in these patients. Following the preliminary workup, male or female sex hormones were applied topically in the form of an ointment. The dosage of each application was roughly 4000 R.U. for

women and about 6 to 7 mg. of *methyl testosterone* for men. A shellac base-plate adapted to the patient's jaws was used to hold the ointment in contact with the oral tissues for one half hour three to five times a week. Applications at home were also advised. The total treatment time varied from a few months to two years.

The results were regarded as satisfactory because of the improved appearance of the tissues clinically and the reduction of the inflammatory exudate microscopically. The constant need of estrogen for the proper maintenance of the health of the oral mucosa may explain the relapses when therapy was discontinued or its biologic action nullified in other ways.

### Syphilis of the Mouth

The clinical differentiation of syphilitic lesions of the oral mucosa from nonsyphilitic affections is sometimes difficult for the expert.<sup>16</sup> While the clinical findings and the patient's history may suggest the diagnosis, it is essential to supplement the clinical findings with laboratory studies.

Chancres of the oral mucosa are encountered most frequently at the mucocutaneous junction of the lips, less often on the tongue, buccal mucosa, tonsils, and gums. On the lips they resemble the ordinary penile chancre but in the areas exposed to moisture, maceration, and friction they present a different appearance, making their recognition difficult. They may vary in appearance from small abrasions, soft to the touch and showing little inflammatory reaction, to lesions larger than a hazel-nut which are elevated, ulcerated, definitely indurated, and even fungating. Enlargement and induration of the neighboring lymph nodes, visible as well as palpable, are diagnostic signs of great importance.

The chancre undergoes spontaneous involution after which an apparently symptom-free or quiescent state of syphilis may develop but during which the infecting organisms may still be plentiful in the mouth. Thus while the mouth appears to be clean, it is actually a dangerous source of contamination. Persistent swelling of the satellite lymph node occurring in the form of clumps or chains should be carefully investigated.

The mucous patches may be either single or multiple. They are a constant source of irritation. They are not painful and the patient is often unaware of their existence. These mucous membrane lesions are accompanied usually by a generalized symmetrical polymorphous, nonpruritic ham-colored eruption. The split syphilitic papule of the commissure of the mouth must be differentiated from perleche and riboflavin deficiency.

Syphilitic glossitis is a common oral lesion in tertiary syphilis. In the superficial form of glossitis, there are a few areas of superficial sclerosis. In the deep interstitial type, the lesions occupy the middle of the tongue. There is irregular lobulation, each lobe being separated by a network of grooves of varying depths. Digital palpation demonstrates fibrous induration of the tongue. There are several shades of red color on the dorsal surface. Leukoplakia or epithelioma is often superimposed on these syphilitic lingual changes. Absence of pain is as a general rule characteristic of syphilitic glossitis.

There is some evidence that dental and oral focal infection may cause an exacerbation of certain of the symptoms of syphilis, such as the lightning pain of *tabes dorsalis*. It is important that periapical and periodontal lesions not only be eliminated but prevented. *Bismuth* and *mercury* may cause stoma-

titis, but this condition occurs rarely in an edentulous mouth and it is less likely to be found when the teeth receive expert dental care. Carious teeth should be filled and restored to their anatomic shape before treatment. The tooth should be scaled free of all tartar and thoroughly polished, after which the patient should be instructed in the proper home care of the mouth.

### Dentistry in Industry

Among the varied factors which contribute to the ill health of the worker, dental and oral disease are most constant and affect far greater numbers in all categories of occupation and industry.<sup>17</sup> The worker suffering from an agonizing toothache for hours, sometimes days, who attempts to continue working with high-speed tools or who is engaged in some arduous task is endangering not only his own safety but that of his fellow workmen. The dental health of a worker then is essential to safety in industry.

The industrial dental health services should include clinical and roentgenologic examination, diagnosis, emergency dental care, the treatment and elimination of dental sepsis, the emergency treatment of industrial injuries and the recognition and treatment of oral occupational diseases. The dentist in industry should be on the lookout for the early signs of occupational disease which are characterized by abrasion, erosion, decalcification of the teeth, and inflammation or pigmentation of the soft tissues. Dental health education is also important. It should include adequate and proper instruction in home oral hygiene.

### Nutrition and Vitamins in Relation to Oral Disease

The extensive nutritional survey made by Metcalf<sup>18</sup> and his associates at Norris

Point, Newfoundland, furnishes some estimate of the relative frequency of the oral physical signs suggestive of a nutritional deficiency. Of the 113 men, women, and children studied, nutritional deficiency was apparent in 61 per cent, suggestive in 31 per cent, and questionable or absent in 8 per cent of the group. Diseases of the tongue, lips, buccal mucosa, the teeth, and gums were prominent physical signs suggestive of nutritional deficiency.

The lingual changes consisted of a magenta coloring, fissuring, and varying degrees of papillary change (atrophy and/or hypertrophy). Angular stomatitis was present in 10 per cent of the group studied. Marked dental caries was recorded in 44 per cent of the women, 29 per cent of the children, and 31 per cent of the men. Severe periodontal disease was noted in 26 per cent of the women, 3 per cent of the children (3 to 14 years), and 19 per cent of the men.

Subjective symptoms related to diseases of the oral cavity and its contained structures were next in frequency to those associated with the eyes. Multiple deficiencies were the rule and those most frequently encountered were vitamin A, riboflavin, and iron deficiencies in the women and children; vitamin A and riboflavin deficiency in the men.

Experimental studies made on rats have shown that pantothenic acid has a profound influence on the oral mucosa.<sup>19</sup> Hyperkeratosis of the enamel and mouth epithelium, at times as early as four to twenty-one days of age, is found. Necrosis of these tissues occurs also and the necrotic process may advance to destroy the interdental papillae and the underlying connective tissue down to the crest of the alveolar bone. The alveolar crests were even destroyed in the advanced stages of the process. There

was an unusual lack of inflammatory response. The possible significance of these findings in the production of periodontal lesions in humans has not been determined.

Field *et al.*<sup>20</sup> noted that glossitis and cheilosis were relieved by **calcium pantothenate**. It seems certain that the clinical response was due to the calcium pantothenate treatment since the other fractions of the B complex were given in adequate doses and for sufficient period of time so that a therapeutic effect should have been obtained. This form of glossitis was characterized by atrophy of all papillae and a slightly bluish redness which was darker than the scarlet red of nicotinic acid deficiency. This type of glossitis is characterized by its tendency to recur. It was also found that **pantothenic acid** was necessary for the prevention or cure of cheilosis in some patients.

#### Developmental Dental Defects— Dental Disease in Early Years of Life

The significance of rubella during pregnancy on the production of dental defects in the offspring was studied by Evans.<sup>21</sup> Twenty-three of the thirty-four patients born of mothers with German measles during pregnancy presented one or more dental defects. Five of the twenty-three exhibited only minor disturbances such as a restricted dental arch. The most severe dental defects were found in babies whose mothers had contracted German measles during the "critical" period of dental development—the sixth to seventh week of pregnancy. The incidence of hypoplasia of the deciduous dentition of normal infants is approximately 0.4 per cent, while the incidence in this series was 23.5 per cent. Retardation of eruption of the teeth was the most striking dental abnormality.

Experimentally, it has been shown by Warkany<sup>22</sup> that maternal dietary deficiencies can induce tooth and jaw changes in the offspring. These include a shortening of the mandible and cleft palate formation along with various changes in the arrangement of the tooth-forming tissues. Bourgoyne and Weber<sup>23</sup> have also observed that children who were born prematurely, or at birth, were exceedingly small, have deformities of the dental arches, teeth, or their relations. There appear to be more deformities in the teeth and their positions in the arches than in any other organ or part of the body.

Sanford and Shnigelsky<sup>24</sup> reported their experiences with purulent parotitis in the newborn. They believe that purulent parotitis is seen frequently enough to warrant a more general knowledge of its diagnosis and treatment. *Staphylococcus aureus hemolyticus* was the responsible organism. It could not be determined whether the infection was from the mouth or whether it was of hematogenous origin.

All cases presented an unexplained rise in temperature (101° to 104° F.) between the fourth to twelfth day of life. Within twenty-four hours there was swelling with heat and redness of the parotid gland. A leukocytosis of 18,000 to 40,000 per cmm. was present. Treatment consisted of **sulfathiazole**, 0.13 gm. per pound in twenty-four hours in four doses. As soon as fluctuation was observed, a small incision was made at the lower border of the gland over the angle of the jaw. The pus pockets were evacuated and an iodoform drain inserted for forty-eight hours. Healing was usually prompt, leaving a small scar that was imperceptible after a few months. Salivary fistulae did not develop. There were no fatalities. In about one third of the cases, the opposite parotid and vari-

ous cervical glands became infected over a period of from two to three weeks.

There is a general misconception of the significance of oral anomalies and laryngeal involvement in speech disorders. Most surprising is the comparative unimportance of anomalies of the tongue. This organ can be completely extirpated without greatly interfering with speech. Tongue-tie, which is not a serious anomaly, is comparatively rare. Greene<sup>25</sup> saw only 12 cases in over 40,000 speech sufferers examined.

Clefts of the palate are much more common and they have a more serious effect on speech. Regardless of the success of operative procedure for cleft palate closure, speech training is required. Speech abnormalities may seriously handicap the individual in his personal or business relations.

### Oral Medicine Actinomycosis

At least two favorable reports on the use of *penicillin* in the treatment of actinomycosis have appeared. McCrea *et al.*<sup>26</sup> and Hendrickson *et al.*<sup>27</sup> reported favorably on the use of penicillin in the treatment of actinomycosis of the cervicofacial region. The case reported by the first group of clinicians had failed to respond to *sulfadiazine* therapy and small doses of penicillin totaling 480,000 units over a considerable period of time were also ineffective.

It was decided that the patient should be given 7,000,000 units of penicillin over a period of 14 days. There was a marked decrease in the swelling and discharge from the draining sinuses at the end of ninety-six hours. Improvement was continuous and when the patient was examined five months later, the skin around the sinuses and operative scars was completely normal. There were no enlarged lymph nodes.

Hendrickson *et al.* treated two cases of actinomycosis without the use of surgical drainage. One hundred thousand Oxford units of penicillin were given every twenty-four hours by intravenous drip in 5 per cent glucose in isotonic sodium chloride solution. Early in the course of treatment 10,000 units in 2 cc. of isotonic sodium chloride were injected directly into the mass after a small quantity of pus had been aspirated. The course of treatment lasted sixteen days and a total of 2,000,000 units of penicillin was administered. Hot wet compresses were applied to the jaw during most of the time.

Within forty-eight hours after the initial dose of penicillin, there was a decrease in the local induration and tenderness. On discharge on the eighteenth day, only a localized nontender indurated area remained with minimal limitation of motion of the mandible. The authors believed that the diagnosis of actinomycosis should be attempted by aspiration of fluctuant areas in a suspected lesion rather than by open drainage.

### Granulopenia—Malignant Neutropenia

New therapeutic procedures are often associated with undesirable side actions. Gingivitis and stomatitis are early and common symptoms of malignant neutropenia. Because of the localization of the lesions, the patients frequently consult first the dentist. All of the sulfonamide derivatives may produce severe neutropenia. Ziegler *et al.*<sup>28</sup> observed a fatal case of malignant neutropenia which followed sulfadiazine administration.

The use of *thiouracil* has been associated with considerable degrees of granulopenia and true malignant neutropenia. Fishberg and Vorzimer<sup>29</sup> encountered granulopenia in 20 per cent of their patients who were receiving this drug.

True agranulocytosis was also observed. **Pyridoxine hydrochloride**, 150 mg. daily by mouth or 200 mg. intravenously, is effective therapy where a severe drop in the leukocyte count has taken place. (The topical application of **penicillin**, 5000 Oxford units per cc. physiologic saline, or the use of penicillin chewing wafers, Topicillin-Squibb, has been shown to be effective local therapy for the painful mouth lesions.—L.W.B.)

About 1½ per cent of Williams and Clute's<sup>30</sup> patients developed agranulocytosis. In addition to the oral lesions associated with this disease, they observed that there was a characteristic enlargement of the submaxillary glands. They also observed that a number of the patients had dental abscesses develop or become activated while taking thiouracil. Herrell and Kennedy<sup>31</sup> found that penicillin was effective in the treatment of severe cellulitis of the mouth and tongue which was complicated by agranulocytosis.

Anday and Ferguson<sup>32</sup> studied the effect of tooth extraction on the white cell count in albino rats and rabbits. It was found that in normal animals, tooth extraction results in a transient leukopenia which was then followed by a slight leukocytosis. If the bone marrow of the experimental animals was depressed by the administration of benzol, a much greater depression of the white cell count occurred and it was not followed by a leukocytosis.

If rabbits were treated with adenylic acid prior to tooth extraction, there was a leukocytosis immediately after tooth extraction which was more marked than in the control animals. Pentnucleotides gave variable results depending on the time it was administered. Pyridoxine hydrochloride was not studied. Splenectomy produced little variation from the findings obtained in normal animals.

The authors could not explain the leukopenia which followed tooth extraction since abdominal surgery or merely a skin incision induced an immediate leukocytosis without a preceding leukopenia. They suggest that the close proximity of the bone marrow to the alveoli may be responsible for this distinction. This study has significant clinical implications as it is known that there are numerous instances where tooth extraction preceded the development of agranulocytosis. Initial clinical studies have shown that the white cell count drops immediately after extraction. Further studies are in progress.

### Allergy

With the more widespread use of methyl methacrylate as a denture base material, the possible allergenic and sensitizing properties of this material assume greater importance. Speakman *et al.*<sup>33</sup> found that the pigmented denture materials were not irritating to the skin or connective tissue. While the monomeric methyl methacrylate produced sensitivity in approximately 20 per cent of the subjects who were tested a second time, the polymeric form (used in denture bases) provoked no signs indicative of irritation or sensitization.

Sassaman<sup>34</sup> reported an unusual case of stomatitis due to sensitivity to *Rhus toxicodendron*. The patient ate several leaves of poison ivy on the advice of friends who told her that this would prevent further attacks. Two days later the patient developed swollen lips, a sore throat, and regional adenopathy. The tongue was swollen and so painful that normal speech was difficult. The gums were hypertrophied and inflamed with shallow erosions on the posterior part of the mouth and the lips. There was superficial necrosis of the palate. The three friends of the patient who also

ate poison ivy leaves experienced no symptoms. The patient was treated with *anesthetic troches* and a 1:1000 *tan-nic acid mouthwash*. On the third day, the oral lesions disappeared. The typical dermatitis appeared on the fourth day.

Albers-Schönberg disease presents striking manifestations in the face and jaw region as a part of the generalized osteosclerotic changes. Winter<sup>35</sup> found that the teeth usually erupt late and they become carious early. The delayed eruption of the teeth is probably caused by sclerosis of the bones. Hypoplastic teeth, partial anodontia and progressive spreading of the teeth are often observed.

Osteomyelitis of the mandible is one of the most dangerous hazards to these patients, often resulting in death. The osseous necrosis has been attributed to constriction of the bony canals of the alveolar arteries, thereby decreasing the blood supply and favoring the spread of infection.

The dental roentgenograms reveal a marked increase in density of the bones of the skull, face, and jaws. There is a marked thickening of the inner and outer tables of the skull. Areas of condensed bone resembling dental roots were visible in the lateral radiographs of the jaws.

Because of the seriousness of dental infection and the difficulties encountered in surgical procedures of the jaws, more cases of this disease should be brought to the attention of the dentist.

### Anterior Poliomyelitis

Aisenberg and Grubb<sup>35</sup> showed experimentally that the virus of poliomyelitis (Creach strain) was absorbed from the exposed vital pulps of monkeys which later developed this disease. They examined the teeth of 375 persons with poliomyelitis and 394 without the disease in the same age groups and geographic

area for evidence of pulpal exposures. The poliomyelitis cases showed an incidence of 65 to 70 per cent pulpal exposures, while the individuals without this disease showed an incidence of 24 to 27 per cent. This difference is statistically significant, being from 3.3 to 5.6 times twice the standard error of difference. It is not the intention of the writers to imply that the exposed pulps of teeth are the only or even the most important portal of entry for the poliomyelitis virus. (There is some question whether elective tooth extractions should be performed during the poliomyelitis season. It is felt that they had better be postponed.—Ed.)

### Erythema Multiforme

The incidence or the clinical recognition of erythema multiforme with oral mucosal involvement appears to be increasing. Duemling and Lesney<sup>37</sup> studied ten cases which presented early and severe oral lesions. They found that the mucous membranes of the mouth and throat may be involved before the general eruption or simultaneously with it. In the mouth, the erythematous macule is rarely observed. The superimposed blebs rupture early to form large desquamated areas on the lips, cheek mucosa, and the margins of the tongue. The tongue margins may show clear-cut indentation markings formed by the teeth. The erosions have a yellowish, necrotic appearance. The oral lesions of erythema multiforme are similar to those of aphthous (herpetic) stomatitis but they do not respond to the usual treatment for "canker sores."

The oral mucosal lesions of erythema multiforme are extremely painful and intravenous feeding of the patient is frequently necessary to maintain nutrition. When the erosions are on or just



inside the vermillion border or exposed to the air, they heal by crusting-over.

Aphthous stomatitis, pemphigus, and syphilis enter into the differential diagnosis. Treatment is largely empiric, inasmuch as a definite causative factor cannot be determined in each case. When the involvement of the mouth is severe and prolonged, parenteral administration of *dextrose* should be given to supplement the diminished fluid intake. Since the disease appears to run a self-limited course, prognosis is usually good, but the prognosis regarding recurrences necessarily varies with the cause.

Stanyon and Warner<sup>38</sup> have noted that these lesions are frequently associated with pneumonia and they have suggested the term "mucosal respiratory syndrome" because of the prostrating febrile illness. In their experience, less than 50 per cent of these patients present skin lesions. They feel that a virus is the probable causative factor because of the negative postmortem bacterial cultures which were obtained from the mucosal and skin lesions, the sputum, blood, and various organs.

Additional cases of histoplasmosis with oral involvement are being recognized. Parson and Zarafonitis<sup>39</sup> reported five cases in which ulceration of the oral mucosa (particularly the tongue) was present. The portal of entry of the fungus could not be determined but there is increasing evidence that the mouth is the most frequent site of entrance. The large number of lesions of the mouth, pharynx, and gastrointestinal tract point to this conclusion.

### **Mandibular Joint Neuralgia and Head Pain**

Facial pain associated with movements of the lower jaw may be a manifestation of temporomandibular joint neuralgia.<sup>40</sup>

The pain may be so severe as to produce a clinical picture of *tic douloureux* or be vague and mild in nature.

The symptoms of temporomandibular joint neuralgia consist commonly of pain in the occipital region, otalgia, glossodynia, and pain about the nose and eyes. In some cases these symptoms are preceded by mandibular joint injury and acute trismus. Loss of the molar teeth without adequate prosthetic replacements may precede by several years the neuralgic symptoms. A history of yawning, biting an apple, receiving a blow, a furuncle in the ear, or ill-fitting dental plates is obtained in other patients prior to the onset of the symptoms.

On roentgenologic study, there may be noted a narrowing of the space between the condyle and the glenoid fossa, either uniform or asymmetric. There is a widening of the joint space and a wide excursion of the condyles. On clinical examination, there may be observed an uneven movement of the lower jaw on opening and closing, crepitus within the mandibular joints, tenderness, and a loss of the usual intermaxillary space due either to abnormal tooth wear or the loss of the molar teeth.

The test of treatment can be determined by means of temporary dental appliances which will aid in restoring the normal intermaxillary space, thereby relieving the pressure on the temporomandibular joints. This phase of dental practice requires both skill and experience.

### **Taste in Denture-Wearing Patients**

Complaints of complete loss of taste are sometimes made by patients wearing full dentures. Less frequently patients wearing partial dentures also complain of some impairment of their sense of taste. Landa<sup>41</sup> found that in the great

majority of cases the artificial dentures were not responsible for this syndrome. Full denture patients are usually of an age at which there is a definite decline of all the physiologic functions, including the senses of taste and smell.

Artificial dentures may be a slight contributory factor to the impairment of taste. The few taste buds (according to some physiologists) present in the palate may be covered by the denture with impairment of taste. Overextension of the upper denture onto the soft palate will neutralize the sensations that might have been derived from the covered taste buds in this area. Lack of cleanliness in artificial dentures also leads to inflammation of the oral mucosa, thereby reducing taste sensation. The continuous and uninterrupted use of strong mouthwashes is undesirable for the same reason.

To alleviate the complaints of loss of taste sensation in full-denture wearers, it is important that the dentures function properly in every respect. Lack of balanced occlusion and articulation leads to trauma with subsequent loss of taste. In rare instances it may be necessary to use a metal base for the upper denture.

While tuberculous scrofuloderma is not as common as in former years, it nevertheless presents a problem in diagnosis and treatment. In Brodsky's<sup>42</sup> experience, the exciting focus, if it be an impacted tooth or a periapical or residual area of infection, must be removed. The cutaneous lesion is then subjected to *grenz ray* therapy. This ray is a very soft x-ray. It exerts a tissue stimulation which permits sufficient local antibody formation to overthrow the invading organisms as well as to assist in establishing a normal physiologic response of the irradiated tissues. The disease process is not only checked but actually cured.

### Maxillary Sinusitis and Dental Disease

McQuiston<sup>43</sup> estimated that from 10 to 20 per cent of all chronic empyemas of the antrum have their origin in infected teeth. The clinical picture of the patient with maxillary sinusitis due to dental infection varies somewhat from that of nasal origin.

In maxillary sinusitis of dental origin, there is no history of preceding rhinitis and there is a tendency for the disease to be unilateral. There is usually a history of dental disease or extractions. In the case of pulpless (nonvital) teeth, the patient may be not be conscious of the trouble. Toothache may or may not be a symptom. The pain is more likely to be confined to the antrum itself and the nasal discharge is scantier. It has the foul odor associated with bone necrosis. General systemic disability is more marked than that seen in maxillary sinusitis of nasal origin. There is also usually clinical and x-ray evidence of dental infection.

The management of maxillary sinusitis of dental origin requires the close cooperation of the dental surgeon and the otolaryngologist. Many dentists attempt to treat the sinus infections by irrigations through the oral fistula produced by the extraction. This type of treatment is often detrimental and may lead to the formation of persistent fistulae which frequently present a considerable problem before closure is attained. These cases become a nasal problem as soon as the dentist is certain that all pathologic dental tissue has been removed.

### Ophthalmology and Dentistry

The interrelationship of ophthalmology and dental infections has been stressed by Spaeth.<sup>44</sup> Iritis is frequently associated with dental foci of infection. Epi-

scleritis and tenovitis have been proved repeatedly as arising in dental foci of infection. In view of our better knowledge of virus diseases, it is doubtful whether herpes ophthalmicus is related to dental disease. Oculomotor conditions connected with a neuritis of the third, fourth, or sixth cranial nerves cannot be so cleanly dismissed. All foci of infection, dental or otherwise, must be cleared up if recovery is to be achieved.

All dental foci of infection should be cleared up before intraocular surgery is performed. Repeated clinical demonstrations, some of them most unfortunate, have proved the correctness and wisdom of this. Unfortunately, neither the dentist nor the ophthalmologist can always state that the dental condition present is responsible for the ocular disease under treatment.

### Pyelitis

The significance of oral foci of infection in relation to many systemic diseases has been minimized in recent years. Heaney and Kretschmer<sup>45</sup> presented evidence which emphasizes the importance of oral foci of infection in the causation of pyelitis of pregnancy. During the last ten years, 9803 deliveries took place at the Presbyterian Hospital at Chicago with a pyelitis incidence of 0.3 per cent. Since other factors responsible for the production of pyelitis remained the same, this reduction was attributed to the eradication of foci of infection before surgical operations and at the beginning of pregnancy.

### Postextraction Bacteremias and Sequelae

The possible systemic effect of the transient bacteremias incident to tooth extraction, particularly in the patient with rheumatic heart disease or joint lesions, cannot be minimized. Bender

and Pressman<sup>46</sup> determined the various factors which might be responsible for these bacteremias and then studied various methods by which they could be controlled.

It was found that actual cautery of the gingival crevice prior to extraction was the most satisfactory form of treatment of the gingival crevice since this area is not only rendered sterile but the capillaries are sealed. This method is satisfactory in single-rooted teeth but, in posterior and multirooted teeth, it is difficult to avoid injury to the adjacent periodontal tissues.

These authors advised that general anesthesia should be avoided and that a *sulfonamide* should be administered twenty-four hours before extraction and from twenty-four to forty-eight hours after extraction in order to assure maximum protection. If sulfanilamide is given, enough should be supplied to raise the blood level higher than 5.0 mg. per 100 centimeters. Sulfanilamide exerts no immediate quantitative effect on bacteremia following extraction, but it does effect a significant quantitative decrease in organisms that have circulated in the blood stream for ten minutes.

Physicians should warn patients known to have rheumatic heart disease about the complications that may follow tooth extraction. These patients should be further advised as to the necessity of both medical and dental supervision during all contemplated dental procedures.

Barnfield<sup>47</sup> reviewed again the subacute bacterial endocarditis dental extraction problem. There remains the question whether or not extractions should be performed in persons with valvular damage. The bearing that the type of anesthetic and the technic of extraction has on the likelihood of endocarditis resulting is not generally appreciated.

There is considerable evidence that premedication with the *sulfanilamide* drugs (or *penicillin*, Ed.) will reduce materially the probability of postextraction bacteremias. Blood levels of less than 3 mg. per cent of sulfathiazole are inefficient. Attention should be directed to the importance of periodontal sepsis in the production of bacteremias following extraction. Attempts to sterilize the gingival crevice, by actual cautery, probably reduce the incidence of post-extraction bacteremias. A higher incidence of bacteremias follows extractions performed under general anesthesia. As a matter of clinical observation, more time and care are used in extraction, and less trauma inflicted when a block local anesthetic is used. Numerous studies have shown that the incidence of post-extraction bacteremias is much lower with local anesthesia.

The possible pathway of fatal infections of the central nervous system and meninges following tooth extraction were reviewed by Haymaker<sup>48</sup> with illustrative case histories. The fatal cerebral complications included subdural brain abscesses, leptomenigitis, suppurative encephalitis, cavernous and lateral sinus thrombosis, and transverse myelitis.

Extractions from the upper jaw were numerically the same as those from the lower jaw. In nineteen of the twenty-eight cases reviewed, only one tooth was extracted, a point which would seem to indicate that the danger lies elsewhere than in multiple extractions. Of the ten cases with spread of the infection to the intracranial cavity *via* the general circulation and one to the spinal cord, there were nine in which only one tooth was removed.

A bacteremia was found to be more frequent after extractions from the lower than from the upper jaw. No correlations could be found between the tooth

extracted and the subsequent clinical course. The tendency for infection in the vicinity of molar teeth to lead to intracranial complications was doubtless due to anatomic relations: Pus arising in the back of the jaw tends to collect between the muscles of mastication and to spread rapidly upward in fascial planes. All nine cases of cavernous sinus thrombosis occurred after the extraction of molars.

Cultural studies revealed a variety of organisms. It was not possible to correlate the organisms with the duration of the illness or the type of lesion produced.

### Salivary—Anti-Infectious Properties

Saliva possesses anti-infectious properties aside from its diluent or flushing action. These anti-infectious properties are also exclusive of any possible antibiotic effects of the oral flora and fauna.

In general, the anti-infectious properties of saliva are comparatively mild compared with the effects of blood serum. *In vitro* tests made by Appleton<sup>49</sup> indicate that saliva has an antibacterial effect on tubercle bacilli. The results of the injections of tubercle bacilli, suspended in saliva, into guinea pigs, indicate that the effect is bacteriostatic and not bacteriocidal.

Some bacteria are agglutinated in saliva. Saliva can, under certain conditions, agglutinate typhoid bacilli but this does not mean that specific, serologic agglutinins are present. Saliva also possesses other interesting properties. For instance, diphtheria antitoxin is secreted in the saliva, saliva accelerates blood coagulation and the subcutaneous injection of human saliva will increase locally the capillary permeability.

The effect of saliva on leukocytes is most interesting. Living leukocytes from the rabbit move *in vitro* toward human

saliva. Centrifuging the saliva, filtering it free from bacteria, or heating it to 132° F. for thirty minutes or more lessened but by no means abolished the chemotactic effect. The significance of this chemotactic influence lies in the importance of leukocytes (particularly as phagocytes) in many pathologic processes. Bacteria which have been exposed to saliva were more susceptible to phagocytosis than were bacteria which had not been exposed to saliva.

### **Sulfonamides in Oral Surgery**

The results obtained by the administration of sulfanilamide or sulfadiazine in cellulitis of the face, neck, or floor of the mouth are usually excellent. Osterloh<sup>50</sup> prefers sulfanilamide in the treatment of severe cases of cellulitis because of the rapidity of its action, thereby preventing general debility of the patient. The use of powdered or crystalline sulfanilamide in tooth extraction wounds has been proven to be actually detrimental to healing in a great majority of cases. Many times there is an actual increase in local irritation and the pain is intensified.

Osterloh also recommends the hospitalization of patients requiring dental extractions who have a history of clinical signs indicative of damage to the cardiac valves from rheumatic fever, syphilis, or a congenital heart defect. An effective blood sulfonamide level should be established before the operation and maintained for thirty-six hours postoperatively.

### **Psychosomatic Aspects of Dental Disease**

Emotional factors are just as important in the causation of dental and oral disease as they are in the causation of disease in other organ systems. Campbell<sup>51</sup> believes that our attitude toward

life can be among the many factors producing dental decay or periodontal disease. A character trait such as rage or undue nervousness, open or disguised, may result in occlusal trauma and consequent paradentosis. On the other hand, fear of oral disease and dental treatment may maintain an anxious tension which will be reflected in one's social relations.

The teeth and paradental structures should be integrated with the total organism, as well as the integration of the patient. The history taking should include not only the disease process being studied but the events in the person's life leading up to its onset.

### **Xerostomia**

Decreased salivary flow is an annoying condition. Faber<sup>52</sup> studied the cause of decreased salivary flow in forty-nine patients. In some, it was due to congenital aplasia, epidemic parotitis, and Mikulicz's syndrome. Roentgen treatment was the cause of decreased salivary secretion in two cases. Pernicious anemia and ariboflavinosis were also causative factors. Fissures of the corners of the mouth, atrophy of the mucous membrane of the tongue, and pain in the tongue were found to be a sequel of the reduced salivary secretion.

### **Carcinoma of Oral Cavity**

Statistical studies made by Beiswanger and Stenstrom<sup>53</sup> indicate that 7 per cent of all fatal cancers in man originate in the oral region. Cancer of the oral cavity is predominantly a disease of old age. The average age in this series was sixty-five years. Chronic irritation is an obvious etiologic factor. The most common irritants are sepsis, dental appliances, syphilis, and the stronger forms of tobacco such as are present in chewing tobacco, snuff, pipe tobacco, and cigars. Ill-fitting dentures have been con-

sidered as a factor only when irritation from this cause extends over a long period, ten to twenty years in most cases, never under five years. In this connection it is interesting to note that in six of the nineteen females of the series, an ill-fitting dental plate was considered to be the causative factor.

Carcinoma of the oral cavity, like all carcinoma, is symptomless in the earliest stages. One half the patients complained of pain as the first symptom, which indicated that the lesion had been present for some time. The other half complained of an ulcer, local swelling, or enlarged cervical lymph nodes. The average duration of the symptoms before the institution of treatment was 8.6 months.

The more malignant lesions appear first as small indurated ulcers or fissure in the mucosa. As the lesion penetrates, pain increases and finally becomes continuous. The more benign lesions, often developing on an area of leukoplakia, appear as a papillary mass. Carcinomas of the floor of the mouth remain infected because of poor drainage. Infection is followed by pain and swelling. Hemorrhage by erosion of an artery may occur.

The differential diagnosis is not too difficult. A biopsy should be done in every case. Other diseases which may form ulcers on the intraoral mucosa are syphilis, tuberculosis, superficially ulcerated or fissured leukoplakia, herpes, and simple granulomas which are caused by trauma. If the Wassermann reaction is positive and the lesion responds to three weeks of intensive antisyphilitic treatment, carcinoma may be ruled out. The two diseases commonly coexist.

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## STREPTOMYCIN, PENICILLIN, AND SULFONAMIDE THERAPY

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### STREPTOMYCIN

Streptomycin, the antibiotic agent produced by *Actinomyces griseus*, was first described in January, 1944, by Waksman and his co-workers<sup>1</sup> at Rutgers University. During the year 1945, this substance was intensively studied as to its pharmacological properties, toxic effects, and as a possible agent for the control of infections resistant to penicillin. Already several reports have appeared which indicate that this new material may prove of value in the treatment of infections caused by certain gram-negative, gram-positive, and acid-fast bacteria.

#### Standardization of Streptomycin

As in the case of penicillin, it is necessary to depend upon biological assays<sup>2</sup> in order to establish standard units of measurement for streptomycin. The units of measurement of this new substance are based upon the inhibition of growth of a standard strain of *E. coli*, this unit being "that amount of material which will inhibit the growth of the particular

strain of *E. coli* in 1 ml. of nutrient broth or other suitable medium."<sup>3</sup> According to Waksman,<sup>3</sup> this unit proved to be satisfactory for production and isolation studies of streptomycin and appeared satisfactory also for pharmacological studies in small animals, but for clinical purposes too many units are required, thus giving the impression that large doses of the material are necessary for assured therapeutic effects. Because of this latter consideration and the fact that the present basis for standardization of penicillin and streptomycin are different, Waksman has proposed the following three units for designating streptomycin:

"1. An S unit, or that amount of material which will inhibit the growth of a standard strain of *E. coli* in 1 ml. of nutrient broth, or other soluble medium. This unit will thus correspond to the original *E. coli* unit.

"2. An L unit, or that amount of material which will inhibit the growth of a standard strain of *E. coli* in 1 liter of medium. An L unit is thus equivalent to 1000 S units.

"3. When crystalline material becomes available, a weight unit will become possible. One can even now prepare for it by recognizing a G unit, comparable to 1 gm. of the crystalline material. Should this material show an activity of 1000 *E. coli* units per 1 mg., it will be equivalent to 1,000,000 S units, to 1000 L units, and 1 G unit, per gm. of material."

Thus far, all of the reported clinical observations dealing with streptomycin have expressed all unit values in terms of S units, or the original *E. coli* unit.

### Absorption, Distribution, and Excretion

Herrell and Nichols,<sup>4</sup> after studying the behavior of streptomycin in man<sup>5</sup> and reviewing similar studies by Elias and Durso,<sup>6</sup> and Zintel and his co-workers,<sup>7</sup> summarize their findings as follows:

"That, following the systemic administration, streptomycin is readily absorbed and reaches the general circulation. It is further evident from these reports that streptomycin, not unlike penicillin, is excreted readily by the kidneys and on occasion half to two thirds of the total amount administered is excreted in the urine within the first twenty-four hours. Following administration of streptomycin by single subcutaneous, intravenous or intramuscular injection, the level in the blood serum reaches a peak in one to two hours and gradually falls off. If repeated injections of 100,000 units of streptomycin are made, it is possible at times to build up concentrations in the blood serum to levels as high as 12 units and in some instances to 25 units of streptomycin per cubic centimeter. It further appears that streptomycin is excreted through the bile. It seems evident, also, that the substance is concentrated in the bile. In human subjects without disease of the

cerebrospinal apparatus, streptomycin does not readily diffuse into the cerebrospinal fluid; however, in the presence of meningitis, amounts sufficient to check the growth of bacteria may reach the cerebrospinal fluid after repeated injections. Likewise, it appears that streptomycin passes rather readily through the placenta and reaches the fetal circulation after its administration to a pregnant woman. After the systemic administration of streptomycin, little or none can be found in the feces. Conversely, when the substance is administered orally little of it diffuses into the blood stream and, therefore, little or none appears in the urine. For this reason, oral administration is not suitable for use in the treatment of infections in general. Streptomycin is not destroyed in the fecal stream and, therefore, it may be used orally in an attempt to rid the intestine of certain organisms susceptible to its action. This property of streptomycin immediately suggests its possible value when given orally in the preparation of patients for operative procedures involving the intestine.

### Methods of Administration and Dosage

*Streptomycin hydrochloride*, or *streptomycin sulfate*, is usually dispensed as a fine powdered substance, in vacuum-packed ampoules, containing 1,000,000 S units of the material. The drug is readily soluble in distilled water, normal saline, and 5 per cent dextrose. The method of administration and dosage of streptomycin varies according to the nature of the disease process treated.

### Administration

**Oral Administration**—As indicated above, streptomycin may be administered by mouth. Since little or no streptomycin reaches the blood stream after



oral administration, this method is limited to those local conditions in the bowel or in certain systemic diseases in which parenteral therapy is supplemented by its use. For this the streptomycin is dissolved in sterile water and mixed with milk or fruit juices and given every three to four hours. Amounts varying from 1,000,000 to 4,000,000 S units are administered by this method.

**Intramuscular Administration**—The intramuscular injection of streptomycin is probably the most satisfactory parenteral method of administration. The drug can be given intermittently every three to four hours in 1 or 2 cc. of distilled water or physiological salt solution containing 100,000 units per cc. For continuous intramuscular administration, the desired daily dosage is dissolved in 500 cc. of salt solution and the rate of flow regulated accordingly.

**Intravenous Administration**—Streptomycin may be given by vein intermittently or by the continuous method. Certainly the intermittent intravenous route is not recommended and, although the continuous intravenous route gives maximum blood levels of the drug, this method is not preferable to the intramuscular route. In order to administer streptomycin by the continuous intravenous route, it is necessary to employ 2 to 3 liters of physiological saline solution containing 1,000,000 to 6,000,000 units of the drug.

**Local Administration**—Following parenteral injection, streptomycin, unlike penicillin, appears well distributed throughout most body fluids. For this reason it may prove that in certain diseases, such as meningitis, it will not be necessary to resort to local therapy. If necessary, however, streptomycin may be given locally.

**Administration by Means of Nebulization**—Streptomycin can be given by

means of nebulization. For this route between 25,000 and 100,000 units of streptomycin per cc. of physiological saline is employed. As much as 1,000,000 units of the material has been given a day without evidence of untoward reaction.

## Observations

**Experimental Observations**—Waksman and his associates<sup>1,8,9</sup> and Robinson and his co-workers<sup>10</sup> have demonstrated that streptomycin possesses high activity *in vitro* against a number of organisms, notably *Escherichia coli*, *Mycobacterium tuberculosis*, *Bacillus mycoides*, *Eberthella typhosa*, *Pseudomonas aeruginosa*, and *Proteus vulgaris*. Furthermore, it was demonstrated that streptomycin was effective *in vivo* against *Salmonella schottmüllerii* and *Brucella abortus* organisms.<sup>9</sup> Heilman has shown that this substance is probably effective against such infections as tularemia,<sup>11</sup> certain spirochetal diseases,<sup>12</sup> and Friedländer's infections.<sup>13</sup> Feldman, Hinshaw, and Manse<sup>14</sup> report striking effects of streptomycin in reversing a potentially lethal tuberculosis in the highly susceptible guinea pig.

Studies on the toxicity of streptomycin in mice were reported by Robinson and Smith and Graessle,<sup>10</sup> and, according to their observations, there was no significant evidence of toxicity.

**Clinical Observations**—Insufficient clinical data do not permit an appraisal of the clinical usefulness of streptomycin at this writing. Nevertheless, it is evident from preliminary reports<sup>4,15-18</sup> in the literature, personal communication to and personal experience of the authors with this new antibiotic agent, that it will no doubt play an important rôle in the control of certain infectious diseases, especially those infections the course of

which penicillin and the sulfonamides have been unable to effect.

Streptomycin will undoubtedly prove to be a most useful urinary antiseptic.<sup>17</sup> Already data are available indicating its effectiveness in such urinary tract infections as *Escherichia coli*, *Pseudomonas aeruginosa*, *Aerobacter aerogenes*, *Proteus ammoniac*, *Streptococcus faecalis*, and the Friedländer organism.

Several types of blood stream infections have been treated with streptomycin. Several cases of *Hemophilus influenzae* bacteremias with meningeal involvement have responded well to the drug. As yet, the results obtained with this substance in the control of brucellosis are promising, but not conclusive. Likewise, the clinical observations dealing with the treatment of acute or chronic *Eberthella typhosa* infections with streptomycin have been on the whole disappointing. Further studies with larger doses of the drug may possibly prove more effective.

In a preliminary report by Hinshaw and Feldman,<sup>18</sup> dealing with the use of streptomycin in cases of pulmonary and extrapulmonary tuberculosis, the authors state:

"From preliminary impressions obtained from the study of thirty-four patients who had tuberculosis and were treated with streptomycin during the past nine months, it appears probable that streptomycin has exerted a limited suppressive effect, especially on some of the more universal types of pulmonary and extrapulmonary tuberculosis in this small series of patients. While the reproduction of *Mycobacterium tuberculosis* may have been temporarily inhibited by the treatment administered, we obtained no convincing evidence of rapidly effective bactericidal action."

In addition to the above, there have been many miscellaneous infections treated with streptomycin with varying success.

However, further clinical studies must be completed before an evaluation can be made regarding the therapeutic value of this new substance.

**Toxic Reactions**—Streptomycin resembles penicillin in its relative lack of toxicity. No doubt systemic reactions will occur more and more infrequently as the purity of this substance is increased. Thus far, no serious untoward reactions have been reported, with the possible exception of a neurotoxic effect in patients receiving large doses of the drug over long periods of time. Several workers<sup>16</sup> have encountered instances of right nerve involvement with resulting transient deafness or disturbance in the vestibular apparatus with severe vertigo.

Occasionally a patient receiving streptomycin will experience a sudden rise in temperature associated with a chilly sensation or an actual shaking chill. At times there also may occur a sudden flushing of the skin, a rapid pulse, and generalized weakness, which reaction is not unlike a histamine reaction.

Urticarial skin eruptions have been seen, following the administration of the drug, and in some are associated with joint and muscle pains.

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## PENICILLIN

Since Fleming reported his discovery of penicillin in 1929, there has been an increasing amount of effort devoted to the isolation and development of similar antagonistic substances elaborated by micro-organisms. Fleming was not the first to suggest the existing antagonism between microscopic forms, for Pasteur and Joubert (1877) reported the inhibiting action of air-borne species upon the growth of anthrax and suggested that this phenomenon might be of value clinically. The first antibiotic substance

as long as six to eight hours after intramuscular injection. While other investigators<sup>43</sup> have reported the use of vasoconstrictors in conjunction with penicillin injections, the advantage of gelatin has not been fully explained. With these methods it is possible to give satisfactory therapy in three daily intramuscular injections. Other investigators, including Cohn *et al.*<sup>44</sup> and Atcheson and Edmeades,<sup>45</sup> utilized oils to reduce the rate of absorption, the former using a water in *oil emulsion* and the latter *peanut oil and beeswax*. Both methods showed prolonged blood and urine levels. Since aluminum in a buffered solution had been used successfully in prolonging the absorption of diphtheria toxoid, Bohls and Cook<sup>46</sup> combined aluminum with penicillin and found that satisfactory blood levels of penicillin could be maintained for six to eight hours following a single administration. They also found that the aluminum was nontoxic and did not interfere with the activity of the penicillin.

Previously reported in this section was the work of Beyer, Flippin, Verwey, and Woodward,<sup>47</sup> who found that para-aminohippuric acid, when given with penicillin, slowed the rate of excretion of the drug. Loewe *et al.*<sup>48</sup> demonstrated that the blood level of penicillin was increased three to six times the control level when the blood para-aminohippuric acid level exceeded 10 mg. per cent. No toxic reactions were noted. Beyer and associates<sup>49</sup> later showed further that the blood level of penicillin in dogs could be increased by the use of the acid and that this substance was not injurious to kidney function. Bronfenbrenner and Favour<sup>50</sup> found that by reducing the fluid and salt intake of the diet and administering benzoic acid by mouth, penicillin serum levels would be increased four to eightfold

with a corresponding prolongation of concentration.

The use of local anesthetics with penicillin to relieve the discomfort of intramuscular injection was reported by Shannon and Zielinski<sup>51</sup> and Lundy and Osterberg.<sup>52</sup> Lahz<sup>53</sup> suggested that an intramuscular needle be left in place for twenty-four to thirty-six hours through which intermittent injections could be made, without the discomfort of repeated skin punctures.

**Oral Administration** - - Penicillin given by mouth has been reported by a great number of investigators. The principal variations have dealt with the dosage and the agent or agents used to protect the penicillin from the gastrointestinal substances which destroy or inactivate the active principle of the drug.

Libby<sup>54</sup> found that large doses of 20,000 to 90,000 units in cottonseed oil in gelatin capsules gave appreciable blood levels, but that absorption was less if the drug was given after a meal than after fasting for eight or more hours. Little and Lamb<sup>55</sup> discovered that by giving penicillin by mouth, mixed with a raw egg, shortly after giving an alkali would give satisfactory and sustained blood levels. This work was repeated in part by Heatley,<sup>56</sup> who concluded that this form of administration might be effective in some clinical diseases, but that the dosage should be at least three times as great as that used for injection therapy.

McDermott *et al.*<sup>57</sup> gave penicillin by mouth in doses of 315,000, 100,000, and 50,000 units in four different mixtures, including corn oil, peanut oil, beeswax, and in water preceded by magnesium trisilicate. There was no significant difference in the results as to what combination was used, although the greater doses gave greater concentrations in each instance. They proposed that the dosage

for oral administration be five times as great as the recommended dose for injection.

Other investigators have used various antacids, including trisodium citrate, disodium phosphate, sodium bicarbonate, hydrous alumina, milk and calcium carbonate, magnesium oxide with hydrous alumina,<sup>58</sup> sodium citrate,<sup>59</sup> aluminum dihydroxy aminoacetate,<sup>60, 61</sup> etc., while protection with oils or greases has been employed by others. The levels obtained and the amount of the drug excreted in the urine have not been greatly altered by any of the adjunctive substances; in fact, the studies of two groups<sup>62, 63</sup> indicate that a simple aqueous solution of the drug gave serum levels and urinary excretion very close to that obtained with a great variety of these antacids and other preparations. Finland *et al.*<sup>63</sup> concluded that oral penicillin therapy should be relegated to those infections in which low doses of parenteral penicillin have proved adequate. Barach and his collaborators<sup>64</sup> have pointed out that with oral penicillin therapy, the feeding interval should be kept constant and suggest that the fat intake be restricted to avoid delay in stomach emptying times. They further point out that the best time to give the drug is one hour before or two hours after feeding.

The use of hardened gelatin capsules and enteric-coated capsules has been reported,<sup>65, 66</sup> but has not given significantly better results than other methods. All investigators agree that feedings should be spaced so that the drug is not given just before or after a meal. It also appears essential that the drug be given frequently in doses varying from three to five times as great as the recommended parenteral therapy dosage.

Clinical trials with oral penicillin have been chiefly concerned with gonorrhea,

pneumonia, and various local streptococcal infections. These diseases have usually responded; however, failures with gonorrhea were usually as high as with sulfonamide therapy.

**Inhalation**—It has been found that penicillin aerosol is therapeutically effective in the treatment of pulmonary disease caused by penicillin-sensitive bacteria, if there has not been extensive anatomical structural change and if the disease is relatively acute. This method also suggests the possibility of routinely administering penicillin by this method, since it is relatively easy and produces little or no discomfort to the patient. Several different methods of inhalation have been suggested and tried clinically. Knott and his associates<sup>67</sup> dispersed penicillin aerosol by means of an electrically driven generator in which the atmosphere of the room was laden with the suspended drug. Tests showed the presence of the drug in the blood serum and in the urine after a fifteen to thirty minutes' exposure to the atmosphere.

Barach and his co-workers<sup>68</sup> nebulized penicillin by passing 5 to 8 liters of oxygen through a nebulizer containing penicillin in concentrations of 20,000 to 100,000 units per cc. Studies on both animals and patients showed that the drug was absorbed in low but adequate therapeutic concentrations. Frequent or continuous administration would seem to be indicated. With this method, four patients with bronchial asthma were relieved for one to two months, following treatment. Other patients with fixed cavitation or advanced pulmonary fibrosis gained little from this form of treatment. Another group<sup>69</sup> also using nebulization, but lower concentrations of penicillin, stated five patients with pneumonia were cured while only half of their asthmatic patients were improved. Three patients had transient fever and

one developed a typical urticaria. Blood levels were low by present standards and the material was found in the urine.

Mutch and Rewell<sup>70</sup> have reported that a nebulized solution of 80,000 units of penicillin per cc., given with oxygen pressure and a close-fitting nosepiece for one-half hour, gave levels equal to those obtained by intramuscular injection.

**Rectal Administration**—Penicillin, incorporated in cocoa butter and given by rectum in doses of 300,000 to 1,000,000 units, was apparently absorbed slowly, giving low but sustained blood levels.<sup>71</sup> This was done on hospitalized patients. This shows that penicillinase does not completely inactivate all penicillin in the rectum.

**Other Routes of Administration**—Intra-arterial administration has been suggested in the treatment of infections of the extremities and is accomplished by injecting 50,000 units of penicillin in 10 cc. of isotonic saline solution into the artery of the part, following which a tourniquet cuff previously placed proximally to the infection is inflated to a pressure of 280 to 300 mm. of mercury and maintained for ten minutes. The authors<sup>72</sup> claim success with a single administration and advise that the method has value in amputation surgery, permitting closure of contaminated wounds.

Bagley<sup>73</sup> suggested injecting penicillin into the knee joint because of its slow absorption from joint cavities. He also recommends injecting the drug about the lymphatics of the affected part, if possible.

**Systemic Administration**—The accepted recommendation for systemic penicillin therapy, as published by the National Research Council and the U. S. Food and Drug Administration<sup>74</sup> still favors the accepted intramuscular route, giving injections every two to four hours with a minimum daily dose of 100,000

units. For serious infections and those with septicemia, a continuous intravenous drip may be advantageous until the acute process is controlled.

**Local Therapy**—Local injection into empyema cavities and intrathecally in meningitis is still recommended but in doses of 50,000 to 100,000 units respectively.<sup>74</sup>

**Topical Therapy**—Many reports on the efficiency of penicillin when locally applied have been reported. The unlimited variable factors and the great ramifications of the results are not particularly convincing. Penicillin is now available in ophthalmic and other ointments, in troches, in dental cones, and in various other forms designed for use in local ulcers, wounds, and other lesions. It is also prepared for nasal sprays. The penicillin in these preparations is sometimes of the unrefined type and may produce sensitization to the impurities.

**Dosage**—As yet it has been impossible to fix the dosage of penicillin, chiefly because of the great variety of diseases treated and the variable response of susceptible organisms. Minimum dosage has been arbitrarily fixed at 100,000 units by Keefer *et al.*<sup>74</sup> for systemic therapy. In serious infections, this dosage should be at least doubled. In the event of oral administration, three to five times the required systemic dose should be used.

**Toxicity**—The principal types of reactions to penicillin have been those of a sensitization nature and those of local discomfort following injection. With the ever-increasing use of penicillin and particularly its use as a topical agent in an unpurified form, the numbers of reactions to the drug will increase. It is, therefore, a wise precaution to use the drug carefully where indicated to avoid extensive contact of the populace with the material. The impurities appear to

TABLE I  
SUSCEPTIBILITY OF THE LIVING AGENTS OF DISEASE TO PENICILLIN

<i>Highly Susceptible</i>		
<i>B. anthracis</i>	<i>Cl. tetanomorphum</i>	<i>R. prowazekii</i> (murine typhus)
<i>B. subtilis</i>	<i>Cl. welchii</i>	<i>Staph. albus</i> (most strains)
<i>Cl. histolyticum</i>	<i>Corynebacterium diphtheriae</i>	<i>Staph. aureus</i> (most strains)
<i>Cl. novyi</i>	Diphtheroid bacilli	<i>Str. bovis</i>
<i>Cl. oedematiens</i>	(most strains)	<i>Str. equinus</i>
<i>Cl. septicum</i>	<i>Diplococcus pneumoniae</i>	<i>Str. hemolyticus</i>
<i>Cl. sordelli</i>	<i>Hemophilus ducreyi</i>	(except group D)
<i>Cl. sporogenes</i>	<i>N. catarrhalis</i>	<i>Str. pyogenes</i>
<i>Cl. tetani</i>	<i>N. gonorrhoeae</i>	<i>Treponema pallidum</i>
	<i>N. intracellularis</i>	
<i>Moderately Susceptible</i>		
<i>Actinomyces bovis</i>	<i>Cl. chauveii</i>	<i>Spirillum minus</i>
Anaerobic streptococci	<i>Erysipelothrix rhusiopathiae</i>	<i>Str. fecalis</i> (enterococcus)
<i>Borrelia novyi</i>	<i>Leptospira icterohemorrhagiae</i>	<i>Str. lactis</i>
<i>Borrelia recurrentis</i>	<i>M. lysodeikticus</i>	<i>Str. nonhemolyticus</i>
<i>Cl. bifementans</i>	Ornithosis virus	<i>Str. salivarius</i>
<i>Cl. botulinum</i>	Psittacosis virus	<i>Str. viridans</i>
<i>Slightly Susceptible or Insusceptible</i>		
<i>Acrobacter aerogenes</i>	Koch-Week's bacillus	<i>S. aertrycke</i>
<i>Alkaligenes fecalis</i>	<i>L. acidophilus</i>	<i>S. cholera-suis</i>
<i>B. mycoides</i>	<i>Listerella monocytogenes</i>	<i>S. enteritidis</i>
<i>Bact. fluorescens</i>	Lymphopathia venereum virus	<i>S. panama</i>
<i>Blastomyces dermatitidis</i>	<i>Micrococcus flauus</i>	<i>S. paratyphi</i>
<i>Br. abortus</i>	<i>Monilia albicans</i>	<i>S. schottmülleri</i>
<i>Br. melitensis</i>	<i>Monilia candida</i>	<i>Serratia marcescens</i>
<i>Br. suis</i>	<i>Monilia krusei</i>	( <i>Bact. prodigiosum</i> )
<i>Coccidioides immitis</i>	Morax-Axenfeld bacillus	<i>Shig. dysenteriae</i>
<i>Corynebacterium acnes</i>	<i>Myc. tuberculosis</i>	<i>Shig. paradysenteriae</i>
<i>Cryptococcus hominis</i>	<i>Past. leptiseptica</i>	<i>Shig. sonnei</i>
"Donovan bodies"	<i>Past. pestis</i>	<i>Str. durans</i>
<i>Eberthella typhosa</i>	<i>Past. tularensis</i>	<i>Str. liquefaciens</i>
<i>Esch. coli</i>	<i>Photobact. fischeri</i>	<i>Streptobacillus moniliformis</i>
Fowl pox virus	<i>Plasmodium relictum</i>	<i>Toxoplasma</i>
<i>Hemophilus influenzae</i>	<i>Plasmodium vivax</i>	<i>Tryp. cruzi</i>
<i>Hemophilus pertussis</i>	Poliomyelitis virus	<i>Tryp. equiperdum</i>
<i>Histoplasma capsulatus</i>	<i>Proteus ammoniae</i>	<i>Tryp. lewisi</i>
Influenza virus (PR 8)	<i>Proteus vulgaris</i>	<i>Tryp. rhodesiense</i>
<i>Kleb. pneumoniae</i>	<i>Ps. aeruginosa</i> ( <i>B. pyocyaneus</i> )	Vaccinia virus
( <i>B. friedländeri</i> )	<i>Ps. fluorescens</i>	<i>Vibrio comma</i>

(Kolmer, J. A., *Penicillin Therapy: Including Tyrothricin and other antibiotic therapy*. New York and London: D. Appleton-Century Co., Inc., 1945, 285 pp. Index and Bib.)

be the cause of reactions, as previously stated. Rostenberg and Welch,<sup>75</sup> in studying the types of hypersensitivity, showed that roughly 5 per cent of individuals who had had no previous contact with penicillin were sensitive. Prausnitz-Kustner passive transfer tests were consistently negative. In some individuals a transient wheal-like reaction of the Arthur type occurred. In testing four brands of penicillin, it was found that three of them gave wheal reactions, while one did not.<sup>76</sup> Several types of sensitivity reactions have been reported, including a bullous dermatitis,<sup>77</sup> stomatitis,<sup>78</sup> dermatitis of the lids,<sup>79</sup> asthma and urticaria.<sup>80</sup> Previously reported convulsions following the application of penicillin to the brain led Walker and Johnson<sup>81</sup> to conduct a series of experiments to evaluate this convulsive factor. Their results showed that the reaction depended in part on the experimental animal used. The factors promoting convulsion seem to be intimately related to the active principle of penicillin. The authors concluded, however, that the convulsive factor should not significantly alter the use of the drug. After massive injections of penicillin into a spina bifida sac of a five-day-old infant, Simon<sup>82</sup> reported that cyanosis followed by convulsions ensued.

Two reports<sup>83, 84</sup> on the etiology of pain following injection of penicillin reveal that as the potency per milligram increases, the pain decreases and that injections into the buttock were the least painful.

**Indications**—The use of penicillin should be preceded by clinical diagnosis and identification of the causative infective micro-organism. This micro-organism should be susceptible to penicillin therapy and, if possible, the individual organism should be tested *in vitro* to determine its resistance or susceptibility.

This procedure will permit correlation of the intensity of treatment with the nature and extent of the disease and the probable effectiveness of the agent upon the etiological agents. In Table I, the susceptibility of the living agents of disease to penicillin is tabulated in a form suitable for clinical usage. In general, penicillin inhibits gram-positive bacteria and the gram-negative micrococci. Recent evidence indicates that it might be of value in the treatment of disease caused by gram-negative bacilli if methionine is added; however, supportive clinical evidence is not yet available.

For practical purposes, it could be stated that penicillin is most decisively effective in those infections produced by bacterial cocci.

**Contraindications**—Also shown in Table I is a list of organisms described as moderately susceptible, slightly susceptible, or insusceptible. Diseases produced by these organisms are not likely to respond to penicillin therapy. Thus far, penicillin does not appear to be of value in the treatment of any disorder other than those produced by micro-organisms sensitive to its effects. It may also be stated that penicillin has not been of value in any of the well-known idiopathic diseases. Faget and Pogge<sup>85</sup> have reported seven cases of leprosy treated with adequate courses of penicillin without appreciable effect. Munter<sup>86</sup> has reported failure of penicillin in pneumonic plague. Similarly, a patient with rabies was treated without effect.<sup>87</sup>

### Recent Clinical Advances

**Pneumonia**—The use of penicillin in the treatment of lobar pneumonia has been at least as effective as the sulfonamides and probably offers certain advantages.<sup>88</sup> The Pneumonia Control Commission of Pennsylvania<sup>89</sup> recommended the use of the sulfonamides in routine

acute pneumococcal and streptococcal pulmonary infections, holding penicillin as an alternate or adjunctive form of therapy if indicated by the individual case. This board further recommended that after sixty hours, penicillin should be given in addition to the sulfonamides if there was no evidence of improvement. They further recommended penicillin as the drug of choice in staphylococcal pneumonia and other pneumonic processes of undetermined etiology. Other investigators<sup>90</sup> feel that penicillin should be used after twenty-four hours of sulfonamide trial without effect and that in the event of an associated bacteremia it should be given initially. The usual recommended dosage of penicillin is 500,000 to 800,000 units, given over a period of five to seven days.<sup>91</sup> The results with penicillin are often more rapid and dramatic than with sulfonamides. Smaller doses of penicillin are often successful, as reported by Kinsman *et al.*,<sup>92</sup> who found that as little as 10,000 units four times daily for four days was adequate. A controlled study of atypical pneumonia by Fleming and Whittaker<sup>93</sup> failed to show any advantage in penicillin therapy. This view was supported by a similar controlled study by Kinsman and his co-workers.<sup>92</sup> Penicillin was administered orally to forty-five patients with pneumococcal pneumonia by Bunn and his associates.<sup>94</sup> Only one death occurred and one patient developed an empyema. Dosage was about five times that given for intramuscular therapy. The authors feel that this form of therapy is equally good as when given by other routes and recommend that treatment be continued for a minimum of seven days. For critically ill patients, they feel the initial dose should be given intramuscularly.

**Empyema**—A great number of reports have appeared illustrating the usefulness

of penicillin in the treatment of thoracic empyema. Investigators<sup>95-99</sup> agree upon closed treatment with frequent aspiration of pus, followed by injection of penicillin, ranging from 10,000 to 100,000 units, with most of them favoring the larger doses. There is no fixed agreement as to the use of concurrent systemic penicillin therapy; however, its use should depend upon the patient's general condition, the state of any concomitant pulmonary disease, and the individual's reaction to the local infection. After adequate closed therapy, it has been found that many of the patients so treated eventually came to surgical drainage.<sup>97,98,100</sup> If diligent care is used in probing pockets of pus and injecting penicillin, it has been our experience and that of others<sup>99</sup> that cures may be obtained. If sterility of the fluid can be maintained, we see no indication to evaluate the pus surgically, since the dead space will heal just as rapidly if closed as if open. In addition, massive contamination is avoided. However, other workers<sup>105,107</sup> feel that the continued presence of pus necessitates open drainage.

**Asthma**—Leopold and Cooke<sup>101</sup> have reported two cases of intractable continuous bronchial asthma, one of which was without symptoms for four months. Twenty-five other patients recently under treatment had already revealed that penicillin was not used. The authors indicate the need of a careful detailed study by many investigators over a long period of time.

**Bronchiectasis**—In the management of bronchiectasis, penicillin is of value in controlling the early disease or the acute exacerbations of the chronic disease; however, it offers little to those with quiescent advanced disease involving fibrosis and marked anatomical distortion of the parenchyma.<sup>102,103</sup> White *et al.*<sup>104</sup>



found the drug of great value as a prophylactic adjunct to pulmonary resection for suppurative lung diseases; however, Blades<sup>105</sup> did not feel that it offered any significant protection.

**Acute Bacterial Endocarditis**—According to Keefer and Anderson,<sup>106</sup> at least 25 to 30 per cent of all cases of acute endocarditis due to the *Staphylococcus aureus*, pneumococcus, or hemolytic streptococcus respond favorably to intensive (200,000 to 300,000 units per day) and prolonged (two to four weeks) penicillin treatment. Not infrequently, valvular damage develops during the course of the disease so that patients may recover from the infection only to show signs of valvular heart disease.

**Subacute Bacterial Endocarditis**—Although large statistics under uniform conditions are not yet available, it appears from preliminary reports<sup>106-116</sup> that approximately 50 to 65 per cent of apparent clinical arrests are being obtained with penicillin in cases of subacute bacterial endocarditis. At this writing it is impossible to make any conclusive statement regarding the amount or route of administration of penicillin for this disease. It is our opinion that all cases of subacute bacterial endocarditis should receive at least 500,000 units a day for at least seven weeks.<sup>115</sup> Early in our experience with penicillin therapy, we employed a continuous intravenous infusion but there is no reason to believe that this method is any more effective than the intermittent intramuscular route. *Heparin* has been used as an adjuvant to penicillin with success by some workers.<sup>108</sup> but in general it is considered that penicillin alone is just as effective and the possible untoward reactions following *heparin* administration are eliminated. As a precaution against reinfection, a careful search for possible foci of infection, such as infected teeth and

tonsils, should be made, and, if surgical procedure is warranted, the patient is given full doses of *sulfonamides*, or preferably penicillin, before and after operation.

**Sinusitis**—Hauser and Work<sup>117</sup> have found penicillin of value in acute sinusitis but point out that the drug is not adequate to eliminate the disease and that surgical treatment cannot be abandoned. They recommend the use of the drug in conjunction with adequate surgical treatment.

**Otitis Media**—Collins and his associates<sup>118</sup> applied penicillin locally in patients with chronic draining ears. Four of nine patients so treated obtained dry sterile ears; however, other methods of treatment proved equally as good. They suggest that greater care be taken to prevent contamination of open ears and that penicillin be used where indicated by the flora of the middle ear.

**Acute Hemolytic Streptococcal Pharyngitis and Tonsillitis**—In a controlled study of forty-five patients with acute hemolytic streptococcal pharyngitis-tonsillitis, Plummer *et al.*<sup>119</sup> found that there was rapid response to penicillin but, if therapy were discontinued too soon, there was a marked tendency toward recurrence. They advised that therapy be continued for at least six days.

**Vincent's Angina**—Reports have shown that penicillin is effective in the treatment of Vincent's stomatitis by either topical or systemic therapy. Pearce and McDonald<sup>120</sup> have reported the treatment of fifty patients with 100,000 units of the drug, given every two to three hours in doses of 10,000 units intramuscularly. Schwartz<sup>121</sup> reported fourteen cases treated in a similar manner. Shallenberger *et al.*<sup>122</sup> treated eleven patients locally alone with equally good results. Schuessler *et al.*<sup>123</sup> feel that

local therapy is superior to systemic methods.

**Ophthalmology**—Numerous reports on the effectiveness of penicillin in infections of and about the eye have appeared. Diseases favorably treated include disseminated choroiditis, acute and chronic iridocyclitis, corneal ulcers, gonorrheal and other acute conjunctivitis, dacrocystitis,<sup>124</sup> epidemic keratoconjunctivitis,<sup>125</sup> meningococcic endophthalmitis,<sup>126</sup> perforating corneal wounds,<sup>127</sup> and trachoma.<sup>128, 129</sup> The drug has been used in several different ways, including systemic administration, local solutions and ointments with iontophoresis, and by means of injection into the chambers of the eye. Systemic therapy has not been found to be as effective as local methods which afford greater local concentrations.

**Scarlet Fever**—A controlled study<sup>130</sup> of thirty-six patients with scarlet fever revealed that penicillin quickly eradicated the streptococci from the nose and throat, but that the drug did not alter the toxic and eruptive manifestations of the disease.

**Meningitis—Pneumococcic Meningitis**—White, Murphy, Lockwood, and Flippin<sup>131</sup> reported fifty cases of pneumococcic meningitis treated with penicillin. The mortality in this group of cases was 64 per cent. This high mortality rate indicated the inadequacy of penicillin alone to control the primary foci of infection. The mortality was somewhat higher in those with bacteremia. All patients received systemic therapy and those who were seriously ill were given continuous intravenous administrations of the drug. Intrathecal penicillin was given in forty-three of the cases. Intracisternal administration appeared superior to other routes. Patients who received only systemic therapy did no better than those who were

given the drug intrathecally. The latter cases were generally more serious. Four patients developed pleocytosis following intrathecal therapy. Considering only those patients who received early and adequate treatment, the mortality was reduced to 42.3 per cent. All but three of the patients had previously received sulfonamide therapy. Sweet *et al.*<sup>132</sup> reported sixteen cases with a mortality of 56 per cent, while Applebaum and Nelson<sup>133</sup> in a series of sixty-seven had a mortality of 61 per cent. White *et al.*<sup>131</sup> suggested a useful plan of treatment including:

1. Prompt diagnosis and ample supportive therapy, including surgery.
2. Penicillin, systemically, 200,000 units daily by continuous intravenous infusion during the acute phase, later by intermittent intramuscular injection, continued until all signs of infection disappeared.
3. Penicillin intracisternally, 10,000 to 20,000 units once or twice daily continued for four days after spinal fluid has cleared and nuchal rigidity decreases.
4. Sulfadiazine or sulfamerazine systemically to a blood level of 15 mg. per cent.

**Meningococcal Meningitis**—Penicillin offers a good alternative therapeutic agent for the sulfonamides. White and his associates<sup>131</sup> reported twelve cases which had failed to respond to sulfonamides. Six of them recovered with penicillin therapy. Rosenberg and Arling<sup>134</sup> reported seventy-one cases with only one death. These cases were treated with penicillin early.

**Streptococcal Meningitis**—Of five cases of streptococcal meningitis treated by White *et al.*,<sup>131</sup> four of them died, three of whom were *in extremis* when treatment was begun, so that no reasonable expectation of success could be entertained.

**Staphylococcal Meningitis**—Four patients with staphylococcal meningitis all recovered. Here penicillin is unquestionably the drug of choice.<sup>131</sup>

**Syphilis**—Numerous reports have appeared during 1945 on the use of penicillin in the treatment of all of the phases of syphilis. At present it is too early to define the position of penicillin therapy in syphilis. Noojin *et al.*<sup>135</sup> reported the prompt response of a case of syphilodema to penicillin therapy. A report from the U. S. Army<sup>136</sup> reveals that the use of penicillin permitted shorter hospitalization with resultant rapid return to duty. In late syphilis, Herxheimer reactions may be serious and should be avoided.<sup>137</sup>

The dangers of inadequate treatment or masking of syphilis by the use of penicillin has been described by Hailey<sup>138</sup> and also by Osmond.<sup>139</sup> The U. S. Army recommendations which were published late in 1945<sup>140</sup> included the following types of syphilis for penicillin therapy: (1) Untreated primary and secondary syphilis; (2) untreated latent syphilis; (3) primary and secondary syphilis which has failed to respond to mapharsen bismuth therapy; (4) primary, secondary, and latent syphilis intolerant of or sensitive to mapharsen-bismuth therapy.

**Psittacosis**—Flippin and his associates<sup>141</sup> have reported a case of psittacosis following a parrot bite. Penicillin therapy was followed in thirty-six hours by definite clinical improvement. It is their opinion that penicillin was of value in this case of psittacosis.

**Rocky Mountain Spotted Fever**—Edmunds<sup>142</sup> reports the successful treatment of a fourteen-year-old boy with Rocky Mountain spotted fever by the use of penicillin; however, Wood and Moore<sup>143</sup> felt that it was not of value in the case they treated.

**Rat Bite Fever**—Altemeier *et al.*<sup>144</sup> have reported three cases of rat bite fever produced by the *Streptobacillus moniliformis*. These patients all responded to penicillin therapy; however, one of them later relapsed, supposedly due to inadequate primary therapy. Penicillin was found to be powerfully bacteriostatic to the three strains of *Streptobacillus moniliformis* recovered.\* Later a report of twenty-five cases of rat bite fever in Michigan, caused by the same organism, appeared. One of these cases died after having had one dose of oxophenarsine hydrochloride.<sup>145</sup> The remaining patients were treated with penicillin and all showed prompt recovery.

**Osteomyelitis**—Altemeier and Helmsworth<sup>146</sup> have reported the primary treatment of thirty-four cases of acute osteomyelitis with penicillin. Twenty-five of the cases were of the acute hematogenous variety, involving major long bones. The remaining nine cases involved pelvic, facial, cranial, and rib bones. They describe four groups of cases. Those in whom early diagnosis and subsequent treatment within three to five days of the onset of the disease uniformly gave good results, in which there was no abscess formation and surgery was not necessitated. This group had an early return to normal function. The second group included those in which diagnosis and treatment were moderately delayed. Surgery was not required, although occasional soft tissue abscesses developed. There was increased bony damage in these, as compared with the first group; however, recalcification occurred without sequestration. In the third group the diagnosis and treatment were delayed from seven to ten days. The infection in these cases was unusually severe with increased bone destruction, associated with large abscesses and sequestration. Prolonged penicillin ther-

apy was required as well as immobilization. In the fourth group they classify the fulminating infection which required early surgical intervention and prolonged penicillin therapy. Dosage varied from 60,000 to 200,000 units daily, given by intermittent intramuscular injection every two to four hours, or continuous intravenous therapy. In small abscesses, pus was aspirated and penicillin injected. Larger cavities were usually drained surgically. In general, the results were excellent. In following the bone changes by x-ray, it was noted that bone destruction is often not present during therapy but reaches its maximum state in one to five months. This is followed by recalcification and revascularization of necrotic bone. Clinical improvement is not usually evident for forty-eight to seventy-eight hours after therapy is begun. With early and adequate penicillin therapy, the authors feel that it is often possible to avoid surgery and eliminate the dangers of secondary infection. Since early diagnosis is often difficult, the authors advocate the immediate use of penicillin in suspected cases without waiting for a diagnosis.

**Hand Infection** In 100 cases of infection of the fingers, Grossmark and Plewes<sup>147</sup> found that topically applied penicillin was adequate therapy if there was no osteomyelitis or suppurative tenosynovitis. This supports the previous work of Florey and Williams.<sup>148</sup>

**Brain Abscesses** Five young adults and a child, three and one-half years of age, with brain abscesses were treated with systemic penicillin therapy in doses of 75,000 units daily, given by intramuscular injection.<sup>149</sup> Drainage was carried out in all cases but the authors give the credit to penicillin therapy. One of the six patients died. The etiological organism in this case was the hemolytic streptococcus. Walker<sup>150</sup> reported one case

that recovered after extensive infection, including osteomyelitis of the cranial bones and widespread suppurative foci. A total of seven operative procedures were carried out.

**Gas Gangrene**—Numerous single case reports of successful penicillin therapy in gas gangrene have appeared. Many of these reports fail to state that *Clostridium welchii* were found or that the other criteria to establish such a diagnosis were present. The report of Fisher, Florey, Grimson, and Williams<sup>151</sup> presented an analysis of 3907 consecutive battle casualties, the results of which should demonstrate that the rôle of penicillin should be to prevent the development of gas gangrene, rather than to treat the established condition. Of 436 patients who had been given penicillin prophylactically, following extensive wounding and contamination, there were only two cases of suspected "gas gangrene" or "gas cellulitis." Of 3471 cases not considered likely to develop gas gangrene and therefore not given prophylactic penicillin, there were five cases of established gas gangrene and twenty-three suspected cases. There were no deaths in the group. Cases were classified into the following four groups:

1. Sixteen cases—A diagnosis of gas gangrene was made on the following clinical and laboratory data: swelling and discoloration of muscle, thin brownish discharge, rapid pulse, low temperature, mental confusion but not usually stupor, and the presence of *Clostridia* on smear and culture. These investigators noted that staphylococci and streptococci were often present. These patients were given penicillin therapy by intramuscular drip and subjected to operative excision of the involved wound, following which they slowly recovered.

2. Thirteen cases—All of which had been suspected of gas gangrene prior to

admission and, with the exception of one, had been given penicillin. It was in this group of cases that gas gangrene did develop and amputation was necessary.

3. Ten cases—All with dirty wounds of three to ten days' duration and all acutely ill. In these, the features of gas gangrene were absent, although all of the wounds showed the presence of clostridia on culture. All of these patients had received penicillin. These cases were ideal for the development of gas gangrene, yet none of them became so infected.

4. These were clean wounds included for the sake of bacteriologic comparison. Macfarlane<sup>152</sup> reported 185 cases of war wounds in which gas gangrene developed. Patients so diagnosed were given penicillin, sulfonamides, and polyvalent serum. There was no essential statistical difference in the mortality of those who received penicillin and those who did not. This offers support to the view that penicillin should be used principally to prevent gas gangrene and not to treat the disease. Langley and Winkelstein<sup>153</sup> reported a study of ninety-six cases of clinical gas gangrene. They concluded that penicillin is not sufficient to control gas gangrene infection, but feel that it has been a helpful adjunct in the management of these cases.

**Surgery**—Penicillin continues to find new uses in surgery. Meleney<sup>154</sup> stated that penicillin in certain cases fulfils all of the criteria for drugs useful in surgical infections, namely: (1) Obviates surgery; (2) limits the extent of surgery required; (3) shortens the period required to control infection; (4) permits primary closure after surgery, or (5) permits earlier secondary closure.

As an example of this, Lamon and Alexander<sup>155</sup> reported closure of decubitus ulcers in a soldier who appeared

to have a transverse myelitis; Bentley *et al.*<sup>156</sup> were able to successfully close sixty of sixty-two compound war wound fractures, which were admitted to their hospital between the third and twentieth day following injury, and similar experiences were reported by Burns and Young,<sup>157</sup> who closed compound fractures of the femurs with equally good results. In other fields, the same usefulness is evidenced by the early repair of neural wounds,<sup>158</sup> the avoidance of puerperal breast abscess formation following acute mastitis,<sup>159</sup> and control of peritonitis following appendiceal perforation.<sup>160</sup>

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## SULFONAMIDES

During the past year, the outstanding contributions in the field of sulfonamide therapy were those dealing with the development of resistant organisms during sulfonamide administration and drug toxicity.

**Development of Sulfonamide-resistant Streptococci**—The use of sulfadiazine in the prevention of respiratory tract bacterial infections in the United States Navy probably represents the largest controlled investigational study ever undertaken. After approximately three months of successful sulfadiazine prophylaxis, the effectiveness of this measure became progressively less in certain areas and eventually a major epidemic of beta hemolytic streptococcic disease occurred.<sup>161</sup> An increase in dosage of the drug did not prevent streptococcic diseases, and it was the impression of medical officers in charge that sulfadiazine had lost its therapeutic effectiveness in these infections. Extensive *in vitro* studies were performed and it was found that the proportion of sulfadiazine-resistant strains was

greater in those receiving the drug prophylactically than in those not getting sulfadiazine. Furthermore, there was some evidence to suggest that in the presence of sulfadiazine-resistant strains, sulfadiazine prophylaxis tended to increase streptococcic infections, particularly scarlet fever.

Damrosch<sup>162</sup> also reported on a controlled program of chemoprophylaxis with sulfadiazine against hemolytic streptococci. During the first period of sulfadiazine prophylaxis, the results were satisfactory, in that significantly fewer streptococcic infections occurred in the group receiving the drug than in the control group. The second period of chemoprophylaxis with a new group of men resulted in a progressive failure to prevent streptococcic infections in the treated group. It was found that this failure was related to the increasing prevalence of the strains of group A hemolytic streptococci which showed *in vitro* resistance to sulfadiazine. As was pointed out by the author: "Regardless of the mechanism of drug resistance, the resulting epidemiologic problems are the same, once resistance strains occur."

**Drug Toxicity** Despite the lack of reliable statistics relating to the number of patients experiencing toxic reactions from the sulfonamides, there are workers in this field who believe the number is increasing each year and that the increase is largely due to the result of induced sensitivity from the local use of these drugs. Today, one of the most widely used forms of therapy is the application of sulfonamide preparations for the relief of dermatologic trivialities.

It is true that there exists among practitioners many with an almost complete lack of appreciation of the real hazards associated with the indiscriminate use of the sulfonamides. However, all of the responsibility does not rest in

the hands of the medical profession, as over-the-counter sale of preparations containing sulfonamides, which practice is allowed in most states, gives rise to widespread self-medication with these drugs. For advertising reasons, sulfonamide drugs are being added to various kinds of salves, tape bandages, shaving creams, and similar products.

Within the past year the New York Academy of Medicine recommended to the City of New York that no sulfonamide preparations be sold without a prescription.<sup>163</sup> This action was prompted because of the fact that the Federal Food and Drug Administration permits the over-the-counter sale of sulfonamide nose drops containing not more than 2.5 per cent of sulfonamide drug and adhesive bandages containing sulfathiazole. This recommendation was made after the responsible committee had come to the conclusion that clinical experience bore out the fact that a small percentage of people become sensitized to the sulfonamide drugs, that a severe systemic reaction may be produced in these persons when the drugs are administered a second time, and that a minute amount of the sulfonamide drugs applied to the unbroken skin or to the mucous membranes can and does sensitize an individual even more quickly and with greater certainty than when such drugs are administered by mouth. Furthermore, because such sensitization is often dangerous and prevents the use of the sulfonamide drugs in treatment of conditions in which they are particularly indicated, because over-the-counter sale of preparations containing sulfonamides will expose many persons to the danger of sensitization, and because the wide use of the sulfonamide drugs in ineffective concentrations may result in an increase in organisms resistant to sulfonamides.

Abramowitz<sup>164</sup> admits that the various preparations containing sulfonamide compounds generally shorten the duration of impetigo, ecthyma, chancroid, and possibly other types of primary and secondary pyodermias, but this advantage is offset by the subsequent complications that may appear. These complications are: (1) Development of a local or generalized dermatitis; (2) appearance of photosensitization to sunlight and ultraviolet rays; (3) interference with the action of the roentgen rays; (4) delay in wound healing time; (5) local sanguineous oozing; (6) interference with the action of sulfonamide compounds by local anesthetics of the procaine series, and the chemically related vitamin para-aminobenzoic acid; (7) resistance to sulfonamide therapy; (8) rendering the patient vulnerable to the subsequent use of the drug when needed. The author believes that wider dissemination of the knowledge of these reactions and consequences is desirable.

Rich<sup>165</sup> has discussed the rôle of hypersensitivity in disease, particularly in periarteritis nodosa. He found widespread periarteritis nodosa in pneumonia patients who died after treatment with antipneumococcus serum and a sulfonamide drug, singly or combined. The evidence pointed to the production of periarteritis nodosa by hypersensitive reactions of the serum sickness type induced by foreign serum or by sulfonamides. Rich states further that since the introduction of sulfonamides in 1936 there has been an increase in the number of cases of periarteritis nodosa coming to necropsy in the Johns Hopkins Hospital. He cautions against the uncontrolled use of sulfonamides for minor ailments and urges that patients under sulfonamide treatment be watched carefully so that the drug may be discon-

tinued immediately on the first appearance of hypersensitivity.

According to Black-Schaffer,<sup>166</sup> the universal use of sulfonamide compounds and the discovery that they can act as antigens capable of eliciting fatal reactions have for the first time made possible the study of a large number of relatively slow but fatal anaphylactic reactions. He describes the lesions discovered in five cases of anaphylactic death following the use of sulfonamides. The basic lesion, as in experimental protein anaphylaxis, is a necrotizing fibrinoid arteritis of the smaller vessels. The cellular exudate was monocytic and the reticulo-endothelial system was hyperplastic. This phenomenon may be the morphologic expression of the addition of some substance to the blood cells that renders them foreign. The possibility that these homologous foreign cells may elicit the production of antibodies was suggested and may account for the hemolytic anemia and agranulocytosis. He pointed out further that the nephrosis in cases of reactions to treatment with sulfonamide compounds is probably a form of anaphylactic renal reaction. The author concluded by stating that the identity of the lesions with those produced in a few human subjects and many animals by known species of foreign proteins, the knowledge that the sulfonamide compounds may convert homologous proteins into allergens and the fact that characteristic clinical syndromes follow the administration of the drugs constitute sufficient evidence to justify the concept of the anaphylactic nature of the lesions described.

According to Kent and Diefendorf,<sup>167</sup> the untoward reactions resulting from the administration of sulfonamides are divided into: (1) Direct toxic effects, such as vomiting; (2) mechanical effects due to precipitation of the drug or its

acetyl derivative in the urinary passages; (3) allergic reactions, such as drug fever and dermatitis. These workers studied 472 patients who received sulfathiazole and of this group 110 showed some form of reaction to the drug with approximately one half of this subgroup exhibiting allergic reactions. Regarding the percentage of patients developing drug fever on any one day during treatment, the authors point out that the curve rises to a peak of 9.9 per cent on the ninth day and thereafter drops abruptly. In other words, if drug fever does not develop within the first nine days of therapy, the chances of its developing on the same administration diminishes rapidly. Of 103 patients receiving sulfathiazole twice, twenty-two patients exhibited sensitivity reactions. Of this number, drug fever occurred within the first two days of readministration in all of the patients who had fever on the first course. Of the patients who reacted to the second administration but not the first, none developed a reaction before nine days had elapsed from the time the first course was started. It was further pointed out that the appearance of sensitivity reactions on the second course is not related to the total time the drug is administered or to the absolute duration of interval between courses. Sensitivity reactions may follow an initial course which may be as short as two or three days. The authors believed that the short time between beginning of readministration and the appearance of drug fever is evidence that an allergic state was present at the time the second course was started. Also, that an interval between courses serves to demonstrate that an initial administration has sensitized an individual to subsequent courses of the drug.

Two cases of acute diffuse hepatic necrosis resulting from sulfadiazine ther-

apy were reported by Herbut and Scariaciotoli.<sup>168</sup> They pointed out that, although focal hepatic necrosis may result from direct clinical action on the liver cells, diffuse hepatic necrosis may be the result of inherent or acquired hypersensitivity of the drug.

Müller<sup>169</sup> discusses seven cases of polyneuritis following sulfonamide treatment. He points out that in general an allergic reaction seems to be responsible for the development of polyneuritis, although in some cases it may result from purely toxic damage to the nerve tissues. It was suggested that previous damage to the nervous system, acholia and thiamin deficiency, may be predisposing factors rendering the patient susceptible to polyneuritis. To prevent the occurrence of polyneuritis, the authors advised that sulfonamide therapy be practiced for as short periods of time as possible and to avoid intermittent administration of the drug. Furthermore, if a patient should develop polyneuritis as a result of sulfonamide therapy, then the patient should never be treated with a sulfonamide drug subsequently.

As a result of wide experience while in military service in North Africa and Italy, Peterkin<sup>170</sup> is of the opinion that the local application of sulfonamides is contraindicated in skin diseases. He qualifies this statement by indicating that if the drugs are used with certain precautions there is but little risk involved. According to this author, of the various sulfonamide drugs employed, sulfanilamide seemed the most apt to cause reactions, especially if used in the form of powder, whereas sulfadiazine appeared to be the safest drug. The whole group seemed less likely to cause reactions if applied in the form of a thick paste or a water miscible cream.

Renal complications continue to be reported in sulfonamide therapy, in spite



of the use of improved forms of the drug. Prien<sup>171</sup> reports two cases of sulfathiazole anuria and uremia in which only focal tubular degeneration was observed microscopically. There was no evidence to indicate mechanical damage from drug crystals or concretions and he suggested a primary chemotoxic cause for the focal lesions in the kidneys. He considers a low urinary output as the most important factor in the causation of kidney complications.

Jepson and Whitby,<sup>172</sup> in discussing *sulfadiazine dysuria*, also stressed the importance of urinary volume. However, they also considered urinary pH of importance, in that they rarely encountered untoward reactions if the urine was maintained at pH 6.5 or over. Prophylaxis depends, therefore, on control of urinary output and urinary pH which can be realized by adequate fluid intake and routine use of alkalis.

Among the various forms of sulfonamide drugs, *microcrystalline* preparations continue to prove effective in certain disease conditions. Frequently the need arises, particularly in the treatment of children, for administration of sulfonamides orally in a liquid form. It is not possible to obtain solutions of the more effective compounds, such as ordinary sulfadiazine, because of their low solubility in water and suspensions, which materials tend to settle out rapidly. In addition, in contrast, microcrystalline preparations of sulfadiazine and sulfathiazole remain suspended for weeks, or even longer, and then appear capable of providing the required fluid dosage form. According to Reinhold, Phillips, and Flippin,<sup>173</sup> *microcrystalline sulfadiazine* is, in addition, absorbed more rapidly than ordinary sulfadiazine from the gastrointestinal tract.

*Microcrystalline sulfonamides* have been employed locally. Ornston<sup>174</sup>

pointed out that *microcrystals* of *sulfathiazole* in operative wounds resulted in less damage and tissue reactions and tended to accelerate healing. No foreign body reactions were observed, according to this worker. Pierce and his associates<sup>175</sup> describe experiments which revealed that sulfathiazole introduced in the form of microcrystals was more rapidly absorbed from the peritoneal cavity than was *crystalline sulfathiazole*.

During the past year, more reports appeared concerning the use of *sulfamerazine* in a variety of infections. Volini, Engbring, and Schorsch<sup>176</sup> used the drug in 200 patients suffering with pneumonia. They found that sulfamerazine was more rapidly and more completely absorbed from the gastrointestinal tract and more slowly excreted by the kidneys than sulfadiazine. Therapeutic blood concentrations of the drug were maintained on smaller doses less frequently administered. Furthermore, the toxic reactions were fewer than with sulfadiazine, probably as a result of the smaller total amounts of the drug required. It was considered by these workers that sulfamerazine offers definite advantages over sulfadiazine and possesses equal therapeutic effectiveness. Genecin, Ausrian, and Nelson<sup>177</sup> report a group of 256 cases of pneumococcal pneumonia treated with sulfamerazine with a mortality rate of only 5.4 per cent.

Reinhold and associates<sup>178</sup> reported on a study evaluating the response of patients suffering with meningococcal meningitis. This study was undertaken to evaluate the response of patients suffering with meningococcal meningitis to treatment with sulfamerazine, with particular reference to the concentration of this drug in body fluids. The results make it possible to define more clearly the advantages of high as compared with low concentrations of sulfamerazine in

body fluids in the treatment of this disease. The concentration of sulfamerazine in cerebrospinal fluid of patients with meningococcic meningitis was found to be approximately 80 per cent of that of an ultrafiltrate of plasma. The authors believe this close relationship shows that factors determining the ultrafiltrability of *sulfamerazine* in serum are also predominantly those that govern concentration in the cerebrospinal fluid. For each milligram of increase in plasma sulfamerazine concentration, the average patient response was found to be shortened by one day. These results suggest that the dosage commonly used is suboptimal and that further trials with therapeutic concentrations in blood serum above 20 mg. per 100 cc. are needed. Furthermore, certain toxic manifestations (drug fever) of sulfamerazine appear to be more frequent at higher concentrations of drug in plasma. Others (rash, hematuria) showed no such relationship. The incidence of toxic manifestations increased appreciably after one week of treatment, reaching a maximum about ten days after treatment was started.

Coggeshall, Martin, and Bates<sup>170</sup> pointed out that *sulfadiazine* is of no value in preventing relapses in the strain of *Plasmodium vivax* naturally acquired in the Southwest Pacific area and deserves no place in the therapy of this type of malaria. This report comes at a time when interest in malaria has been stimulated in this country by the high incidence of relapsing malaria, especially *P. vivax* in troops returning from service in endemic malaria areas.

Corper and Cohn<sup>180</sup> discussed the use of sulfones and sulfonamides in the treatment of tuberculosis. These workers stressed the point that the beneficial effect from these compounds is attributable to their toxicity—namely, anoxia and anoxemia. In view of the greater

sensitivity of the human being to these effects and the fact that such a mechanism appears to explain the favorable results noted in experimental tuberculosis, it would not seem warranted to continue human experimentation with these drugs at present, particularly in the tuberculous individual. Furthermore, all of the necessary information for proper evaluation can be obtained from careful animal experimentation.

Not infrequently it is important that we know whether a patient has been receiving a sulfonamide drug or not. This information is of particular value in cases of suspected sulfonamide toxicity, such as drug fever. LaRosa<sup>181</sup> has described a rapid and simplified test for estimation of sulfonamides. By the use of test paper containing Ehrlich's reagent with a sufficient quantity of oxalic acid to give a pH of 2.5 when wet with serum or other biological fluids, the level of sulfonamides can be estimated directly in plasma, serum, and other clear body fluids without the addition of precipitating or acidifying agents. The orange color produced is evaluated by comparison with an appropriate color chart, or with colors produced simultaneously from solutions of known concentration. The test paper can be prepared from a good grade of white absorbent paper.

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## THERAPEUTICS

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### Radioactive Phosphorus

With the end of World War II, it is likely that radioactive materials of various sorts will find useful places as therapeutic and diagnostic agents. Of these substances to date, radioactive phosphorus has been the most widely used and useful.

Warren<sup>1</sup> reported recently on the therapeutic use of radioactive phosphorus in eighty-one cases, and referred to

other series that have been reported. Various methods are used to produce radioactive phosphorus and various degrees of radioactivity are possible in the product produced by different methods. Essentially, radioactive phosphorus is produced by bombardment by the cyclotron; the difference in the position and the type of phosphorus used accounts for a difference in the activity in the products produced. Only a portion of the phos-

phorus in the material exposed becomes radioactive. Radioactive phosphorus has a half life of 14.3 days with a steady rate of decay. The material can be treated chemically and is usually converted to dibasic sodium phosphate, which does not alter the radioactivity.  $P^{32}$ , or radioactive phosphorus, is finally converted to sulfur by the loss of its electron as beta radiation. The half life of 14.3 days permits manipulation and administration of radioactive phosphorus before excessive loss of radioactivity and yet continues radioactivity only long enough to be therapeutically effective and not long enough, under careful control, to produce serious radiation damage.

Warren reported the use of  $P^{32}$  in three forms, as dibasic sodium phosphate, magnesium ammonium phosphate, and phosphoric acid. Two routes of administration were used in Warren's cases, intravenously, with the dose of  $P^{32}$  being dissolved in 300 cc. normal salt solution and 5 per cent glucose. When given orally, it was dissolved in orange juice. It was noted that in the oral administration, 20 to 30 per cent of the dose was lost due to precipitation as insoluble phosphates in the gastrointestinal tract. The intravenous route was preferred. The selection of the eighty-one cases included diseases known to be highly radiosensitive, some of which had become resistant to roentgen radiation. The eighty-one cases included chronic myelogenous leukemia, subacute myelogenous leukemia, acute myelogenous leukemia, chronic lymphatic leukemia, subacute lymphatic leukemia, acute lymphatic leukemia, monocytic leukemia, acute leukemia, unclassified, lymphosarcoma, plasma cell leukemia, plasmacytoma, Hodgkin's disease, polycythemia vera, and blood dyscrasia, unclassified.

Dosage in the cases reported varied between 600 microcurie to over 4000

microcurie. No harm seemed to have occurred as a result of the doses administered. Attention was called to the fact that if there is extreme leukemic infiltration of the marrow, radiation will change a leukemic marrow to aplastic marrow. For this reason, sternal marrow study is advocated. It was further found that internal radiation therapy from  $P^{32}$  may give further temporary relief to roentgen-fast cases. Radiation sickness was rarely encountered. About one third of these cases, which had initially extremely poor prognosis, showed temporary improvement.

Polycythemia vera responds almost specifically or at least more specifically than to any other form of therapy. Hall *et al.*<sup>2</sup> reported twelve cases of polycythemia and mentioned that forty-five cases have been adequately recorded in the literature where radioactive phosphorus has been used. The dosage of  $P^{32}$  used in these twelve cases varied from 15 to 2 millicurie given in from one to three injections. They cite that the ease of administration, lack of sickness or toxic symptoms and the effective delivery of radiation to the marrow cells makes radioactive phosphorus a therapeutical choice in polycythemia.

### Salicylates, Mode of Administration, Dosage, Toxicity

Physiologic effects of salicylates have an abiding interest to most practitioners. Other than the almost specific effect commonly observed in rheumatic fever, they are used widely for their analgesic and antipyretic effects. Within the past few years, new conceptions have arisen regarding this drug.

The effective dose in rheumatic fever was brought to attention by Coburn and others (1943) and has been previously discussed in this column. The effect of salicylates upon the prothrom-

TABLE I  
RESULTS OF THERAPY

Type	Previous roentgen-ray therapy	Number of cases	Number helped	Per cent helped
Chronic myelogenous leukemia.....	—	9	5	56
	+	10	4	40
Subacute myelogenous leukemia.....	—	2	2	100
	+	0	0	0
Acute myelogenous leukemia.....	—	8	0	0
	+	1	0	0
Chronic lymphatic leukemia.....	—	3	1	33
	+	5	4	80
Subacute lymphatic leukemia.....	—	2	0	0
	+	2	1	50
Acute lymphatic leukemia.....	—	8	1	13
	+	4	2	50
Monocytic leukemia . . . . .	—	4	1	25
	+	0	0	0
Acute leukemia, unclassified . . . . .	—	8	0	0
	+	0	0	0
Lymphosarcoma . . . . .	—	2	0	0
	+	2	0	0
Plasma cell leukemia . . . . .	—	0	0	0
	+	1	0	0
Plasmacytoma . . . . .	—	0	0	0
	+	3	2	67
Hodgkin's disease . . . . .	—	0	0	0
	+	3	1	33
Polycythemia vera . . . . .	—	3*	2	67
Blood dyscrasia, unclassified . . . . .	..	..	..	..
	—	—	—	—
Total . . . . .	..	81	27	33

bin time has also been previously discussed and was brought to attention effectively by Link and his associates (1943). It has been the experience of several observers that there was no appreciably greater benefit from intravenous administration of salicylates. Reactions with this drug have been more common than previously reported. It seems quite likely that large doses by mouth have adequate beneficial effect (60 to 120 grains per diem) and less toxic reaction than similar dosages given intravenously.

Butt *et al.*,<sup>3</sup> running control experiments in a group of Navy personnel,

helped to clarify some of the rather vague impressions existing regarding salicylate therapy. Daily doses of 3.2 gm. (50 grains) did not affect the prothrombin time. However, when the dosage reached 10 gm. (150 grains), there was an appreciable increase in the prothrombin time of a reasonable percentage. Sodium bicarbonate did not alter the effect upon the prothrombin time. The salicylate blood level determined upon serum was found to be between 30 and 50 mg. per 100 cc. during the period of dosage of 10 gm. (150 grains) daily. No hemorrhagic manifestations were noted at that time. The effect on

the hepatic parenchyma was discussed and it was concluded that with the available liver function studies, little, if any, harmful effect could be detected; however, it is known that the salicyl radical is not altered in the liver.

The sedimentation rates in patients with recurrent attacks of rheumatic fever do not respond to salicylate therapy with any degree of uniformity. No consistent change in the urine was observed and there was no albuminuria noted.

Taran and Jacobs<sup>4</sup> reported excellent results with massive doses of salicylates. They noted distinctly more effective results with larger doses in children. They found that the oral route was as satisfactory and effective as the intravenous route. Their dosage was calculated on the basis of 0.1 gm. ( $1\frac{1}{2}$  grains) sodium salicylate per pound of body weight by mouth daily and, at times, whatever increase was necessary to raise the blood plasma salicylate to between 300 to 450 gammas per cc. There were no hemorrhages or hemorrhagic manifestations observed. All patients suffered from severe tinnitus, some vomited and had disturbed appetites. These complications did not interrupt therapy in any instance.

Manifestations of salicylism, as reported by Caravati and Whims,<sup>5</sup> occurred in the following order: Tinnitus, dizziness, nausea and vomiting, fever, hyperpnea, and cephalopathy. They suggest that the major effects, those on the respiratory system, vasomotor system, and gastrointestinal tract are due to the salicyl radical in the higher centers, the action being similar to that of ketone bodies. Mental changes, such as excitation, dulness, lethargy, confusion, delirium, restlessness, incoherent speech, mania or hallucinations, can occur. All of the above effects are probably due to prolonged massive dosage. When the blood level of salicylism is maintained

for prolonged periods above 360 gammas per cc., the authors advocate a reserving administration of alkali for the treatment of toxicity salicylism rather than its concomitant administration with salicylates. They outline the treatment for salicylism which includes the following: (1) Withdrawal of salicylates; (2) large doses of bicarbonate of soda; (3) adequate fluids, parenterally, if necessary; (4) cooling measures when fever is excessive; (5) adequate caloric intake; (6) caffeine or ephedrine to combat central depression.

This discussion does not include the occasional anaphylactic reaction which can occur from a single aspirin tablet as well as from massive salicylate therapy.

### Benadryl

Benadryl is a newly synthesized antihistamine drug produced by Parke, Davis & Company. Members of the staff at Mayo Clinic<sup>6-11</sup> reported studies of the drug in November, 1945. The chemical name is beta dimethylaminoethyl benzhydryl ether hydrochloride. In its physical properties, benadryl is a white crystalline powder, soluble in alcohol and water. It is much more active than aminophylline in relieving bronchial constriction caused by histamine shock in animals and many more times effective than papaverine in antagonizing histamine effects upon the gastrointestinal tract. The most important observation seems to be its property to neutralize histamine effect in the system.

Benadryl's toxic effects were studied in animals and have been reported as follows: Lethal doses show excitement, convulsions, respiratory failure, and death. Toxic sublethal doses produce ataxia and excitement. No changes in animals were noted in the blood counts or non-protein nitrogen levels.



McElin and Horton,<sup>6</sup> administering the drug by oral, intramuscular, and intravenous routes, demonstrated histamine action of the following types: (1) Decrease in the cutaneous vasodilating action of histamine; (2) alleviation of nasal congestion caused by histamine; (3) decrease in gastric acids and the volume of gastric secretion provoked by the administration of histamine; (4) depression of the wheal and flare response in a case of hypersensitiveness to cold.

The report of their treatment of patients includes eighty-one cases. Most of these were various allergic conditions, such as asthma, hay fever, urticaria, Ménière's syndrome, or painful conditions, possibly or probably due to histamine effect. Of these, excellent results were obtained in hay fever, urticaria and angioneurotic edema, tension, and headache, with vasodilating features. Relatively poor effects were found in asthma, well-established Ménière's disease, migraine, and various painful conditions throughout the body.

Benadryl can be administered orally, intramuscularly, or intravenously. Orally, the dosage varies from 50 to 500 mg. per day; intramuscularly, 20 mg. per injection; intravenously, 10 to 120 mg. by continuous intravenous drip within ten minutes. The dilution for intravenous administration used by the authors was 60 mg. of benadryl per 100 cc. of normal saline solution.

McElin and Horton report excellent results in treating the urticaria and edema associated with sensitivity to the administration of penicillin and barbiturates.

The writer has had one failure in eleven cases of urticaria and this case was, in all likelihood, a reaction to sulfanilamide administration. The dose of benadryl did not exceed 300 mg. in

forty-eight hours and, therefore, may have been inadequate dosage.

In addition to the use in urticaria, it has been successfully used in two cases of allergic eczema and a case of urticaria without skin lesions or changes thought to be psychogenic in origin. One case of migraine was relieved in that customary duration of attacks were shortened by two days. The nausea and vomiting were eliminated after a trial for two months, in which there were six attacks treated. The drug was lacking during one attack and this attack persisted for the usual three-day duration.

The side effects, while not of a serious nature, consisted of sleepiness, dizziness, mental sluggishness, dry mouth, tinnitus, and nausea. In certain instances where the hives or urticaria were minimal, the patient preferred to suffer the inconvenience rather than feel the effects of benadryl. However, the drug provided phenomenal and distinct relief to nearly every acute or chronic case of urticaria with severe symptoms and promises to be a potent factor in the relief of urticaria and hay fever. Because of its mode of action, there are implications that it will be considered in the relief of gastric ulcer, gastrointestinal spasm, and certain forms of edema and possibly other sensitivity states.

### Red Blood Cell Derivatives in Protein Replacement

In the work of Strumia *et al.*,<sup>12</sup> in the preparation of modified globin from human erythrocytes, it was found and conclusively proven that this substance could replace the colloidal osmotic properties of plasma in administration to human subject. Therefore its value in shock, hemorrhage and hypoproteinemic states, restoring with marked effectiveness the oncotic pressure, maintaining and restoring the lost blood volume. The ques-

tion remained, after the original report of the above authors, as to its ability to act as a substitute in a nutritional way for body proteins. Miller *et al.*<sup>13</sup> reported interesting experimental work bearing on this subject. A breakdown of hemoglobin indicates a basic protein, having a low content of essential amino acids, isoleucine and methionine, with a pigment radical and iron. Globin forms 96 per cent of the hemoglobin of the red cell, the remainder being iron attached to a pigment material, protoporphyrin. The method used by Miller *et al.* consisted of preparing hypoproteinemic dogs by fasting and low protein diets. These dogs were injected with laked red blood cells. The result indicated that no new plasma proteins are formed. However, nitrogen balance was maintained even in the face of high protein excretion in the urine.

In order to effectively replenish the protein pool, amino acids have to be drawn from body reserve to form cell or plasma protein. When the laked cells are injected, nitrogen is excreted in the urine in increased amounts, whereas, if plasma protein is injected intraperitoneally, the nitrogen excretion of the urine is not increased and the circulating plasma proteins are elevated.

Double depletion of animals established with frequent bleedings, in addition to the low protein diet, behaved differently when hemoglobin was injected intraperitoneally. These animals produced new plasma protein and new hemoglobin. In this instance, laked red blood cell hemoglobin is completely used. Digests of hemoglobin, given by vein, were proven to maintain nitrogen balance. When doubly depleted dogs were given large amounts of washed red cells intraperitoneally, plasma proteins were produced.

Thus it would appear that where an anemia or need for hemoglobin exists, as well as depleted plasma proteins, there is a greater synthesis in use of hemoglobin from red blood cells administered intraperitoneally, or by vein. This is a sound and significant addition to the mode of the effectiveness of globin. Globin, unlike the digest of laked cells, is a purer protein, and does not cause the reaction sometimes incurred by injection of whole red cells, or digests of red cells.

It is quite likely from this and other observations that globin, under certain circumstances, can, in addition to its other properties, (1) maintain normal nitrogen balance; (2) in anemic and hypoproteinemic states, possibly aid in regeneration of the body protein.

#### **Morphine Supplemented by Dextroamphetamine**

Analgesia, produced by morphine, supplemented with dextroamphetamine, was studied by Ivy *et al.*<sup>14</sup> The analgesic effect was studied by pain threshold and records were made of blood pressure, pulse rate, choice reaction time and flicker fusion frequency before and at thirty-minute intervals for two and one-half hours on twenty-one subjects. There was a significant rise in the pain threshold when dextroamphetamine was administered with morphine as compared to morphine administered alone. The dose of the morphine sulfate administered alone was 16 mg. When combined with dextroamphetamine, the dosage was morphine sulfate, 16 mg., and dextroamphetamine, 20 mg. The administration was by subcutaneous injection. This combination of drugs gave a definite increase in the overall elevation of pain threshold and a delay in reactions to the depressing effect of morphine, as compared to morphine given alone. This

did not occur in all subjects and in certain instances, in both morphine alone and morphine and dextroamphetamine, there was a lowering of the pain threshold. However, percentagewise, as stated above, morphine and dextroamphetamine were superior to morphine alone in raising the pain threshold.

When dextroamphetamine was combined with morphine, there was definite rise in systolic and diastolic blood pressure. The pulse rate with morphine alone was reduced, whereas with morphine and dextroamphetamine, it was increased. There was less depression in the combination than with morphine alone. Nausea and vomiting occurred less frequently with the combination and, when it did occur, was delayed in its appearance as compared to time of incidence to the administration of morphine alone. The elevation of the pulse rate and the rise in blood pressure produced by morphine and dextroamphetamine make the combination inadvisable in certain patients with hypertension and possibly those with delirium.

### **Adrenalin in Treatment of Autonomous Anxiety States**

Treatment of persistent anxiety states by means of adrenalin has been proposed after successful trial by Cameron. Where anxiety states developed following severe and persistent mental trauma, such as exposure to trying situations, and working at high tension, it was pointed out that autonomous mechanisms involving the sympathetic nervous system led to its development. Having so reasoned, it was logically proposed that desensitization by some agent capable of providing a similar trauma, in objective fashion, could build up resistance in the human mechanism, thereby breaking the autonomous mechanism of an anxiety state. This was attempted with repeated in-

jections of adrenalin, using both intramuscular and intravenous administration in the original cases.

An intravenous method was developed to overcome objections to the intramuscular method, such as pain, occasional rapid absorption and a persistent state of tension. The intravenous method consisted of establishing a continuous intravenous flow of normal saline, with a three-way stop-cock immediately behind the needle for the administration of adrenalin. A resting period of thirty minutes precedes the injection, during which time pulse rate and blood pressures are recorded. Adrenalin is then administered each ten minutes for four injections. The reaction to the injection consisted of pallor, tremor, changes in the pulse and respiration, and the subjective feeling of the patient. The initial dose is 0.01 mg. As the reaction diminishes, the dose is gradually raised. The bulk of the injection, however, is maintained at a volume of 1 cc. and the speed of injection is maintained at one second.

Patients were treated three times weekly, but it is possible to administer treatment daily. A sixfold increase was the largest obtained in thirty days, with a treatment given three times weekly; this is the usual method followed. The signs of increased tolerance is best determined by lessening of the pallor, tremor and dyspnea following the injection, including the patient's statement that the injection seems milder.

Cameron<sup>15</sup> states that only in patients where the anxiety state has become autonomous is this treatment favorable. Those with obsessive thinking do not respond well, as the failures may be attributed to a continuing etiologic situation. Nineteen cases were reported with completed treatment. Of thirteen patients treated for more than thirty days, nine were reported with good

results and four were reported with transitory or no improvement. The results of the injections themselves consist of tension, anxiety symptoms, paleness of the skin, tremor, etc. As these symptoms disappear, the following happens. The face becomes flushed, extremities become warmer, and there is a feeling of relaxation, sometimes drowsiness and even sleep.

This is an interesting and unusual treatment for certain anxiety states and, if it can be further confirmed by clinical trial, will add an extremely useful method of treatment heretofore refractory to the usual methods.

### **Uses and Efficacy of Parenteral Liver Extracts**

Since the use of liver in the treatment of pernicious anemia has become widespread, there have been preparations of various potencies available. It has not always been clear to the average physician how the various preparations were produced, nor has there been any method better than the trial and error method to determine which of the available preparations provided the best therapy. One would not wish to detract from the excellence of concentrated liver extracts in their efficacy in treating Addisonian anemia. It is probable that no argument will arise to refute the fact that concentrated liver extracts contain a valuable and potent antianemic principle very efficient in the treatment of primary pernicious anemia.

In recent years, there has been a tendency to return to the use of crude liver extracts. The thought behind the use of this principle seems to be that these preparations contained more of the natural constituents of liver; in other words, more B complex fractions and possibly more protein, which added to the anti-

anemic principle a good source for these often needed materials.

A welcome comparison of crude and concentrated preparations has been reported by Clark<sup>16</sup> and certain conclusions are presented which are of value. Random samples of liver extracts conforming to U.S.P. standards were tested for riboflavin, niacin, pantothenic acid, and L. casei factor by microbiologic methods. Choline was not included in the comparison and it was pointed out that thiamine is of negligible content in parenteral liver extracts. It is also apparent that certain stages of the methods of preparation are not openly available. The data obtained by Clark's investigation indicate that crude liver extracts contain on the average less riboflavin, niacin, pantothenic acid, and L. casei factor than do refined concentrated preparations. This investigation apparently definitely refutes an impression that crude liver extract has any distinguishing merit in providing B complex factors.

The difference in the total amount of nitrogen made available by the use of crude extract, as compared with concentrated extract, would hardly be of nutritional value as shown in the analytical data secured in this investigation.

One thing is obvious, that there is little justification for the preferred use of crude liver extracts in the treatment of primary pernicious anemia. It may be that other factors, as yet unknown, account for the clinical impressions that crude liver extract is more efficient in a nutritional manner than concentrated extracts. It would seem apparent that where vitamin B complex is needed, a better source is available than crude liver extract. The cost of crude liver extract may be its only merit in cases where only a few units are needed to maintain cases of primary pernicious anemia.

Where nutritional factors are needed, it is probable that present protein and amino acid hydrolysates are a better source.

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## UROLOGY

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### Anesthesia

Two new drugs have been developed as antispasmodics to be used with or without various types of anesthesia to produce relaxation. One of these is **curare**. This drug is used at times with various anesthetics. When maximum relaxation of the patient seems to be necessary, the anesthetic must be administered at dangerous levels unless a relaxing aid is available. Curare, 1 to 3 cc., is recommended for that purpose. It can be used with any general anesthetic and will produce complete relaxation without placing the patient in a dangerous anesthetic stage. The drug may be used in nephrectomies, abdominal prostatectomies, and other operative procedures where a relaxed abdomen is essential.

Lenahan's<sup>1</sup> technic is as follows: Anesthesia is induced with sodium pentothal-nitrous oxide-oxygen, 50 per cent, or cyclopropane-oxygen. Due to the fact that relaxation is so rapid following intravenous administration, curare is not given until one or two minutes before

the peritoneum is opened or maximum relaxation is necessary. At that time 1 or 2 cc. (20 to 40 mg.) are given intravenously. Wait about three or five minutes and, if necessary, cautiously add an additional 1 or 2 cc. (20 or 40 mg.)

The curare effect persists for about thirty minutes. If necessary, the drug may be repeated preceding closing of the peritoneum; usually half as much will suffice at this time.

If the patient should be more susceptible than the average and paralysis of the diaphragm results, the patient should have an open airway maintained, by intubation if necessary and, by simple manipulation of the bag, oxygenation is maintained. Normal breathing is usually resumed in three to ten minutes.

Carll, Deaver, and Phillips, from the Naval Hospital at Norfolk, report a case in which a patient had been under spinal anesthesia for seventy-five minutes; considerable rigidity was making it difficult to replace the intestine in the peritoneal cavity and close the wound. Intocostin (curare) was injected, the

dose being 60 mg., and within one and a half minutes relaxation was produced which lasted twenty minutes, allowing closure.

They failed to find any circulatory depression and the largest blood pressure drop was 30 mm. of mercury with recovery in about ten minutes.

In their opinion, and in the opinion of others, namely, Cullen, Hudson, and Cole, by substituting curare for spinal anesthesia and using cyclopropane, relaxation is as good as in spinal anesthesia and one avoids the fall in blood pressure, eliminates the headache, nausea, and vomiting, and other untoward signs and complications of spinal anesthesia.

Another relaxing agent that has been developed in the last year to take the place of depropanex is AP-43. AP-43 has been synthesized by the Abbott Laboratories, North Chicago, Illinois. It may be given by mouth, intramuscularly, or intravenously, the dose varying from 50 to 150 mg. Usually one of the barbiturates is used with the drug. It is effective in relieving pain from ureteral catheterization and retrograde pyelography; it aids in the passage of ureteral calculi, and it has been used successfully in the treatment of severe bladder spasm. The trade name, "*amethone*," has been tentatively accepted for AP-43.<sup>2</sup>

In the author's clinic, *pentothal sodium* is the anesthesia of choice. It has been used in all types of major urological surgery and its effects have been so satisfactory that we seldom use any other types of anesthetics. The secret is to combine pentothal sodium with preliminary medication, *morphine* and *atropine*, and to keep the patient in the early stage of the second degree of anesthesia. Curare may be used if necessary for relaxation in the difficult part of the surgical operation. Pentothal sodium has the advantage that it is not

explosive and that it has no serious post-anesthetic complications. As a matter of fact, it has been our experience that the very badly decompensated cardiac patient will leave the operating room with better cardiovascular tone than prior to operation. This anesthetic is particularly valuable in operations where any form of electrosurgical apparatus is being employed.

With spinal anesthesia, a vasopressor agent is usually administered beforehand. If ephedrine is used, it may cause tachycardia, nervousness, and occasionally extrasystoles. Another effective combination used by Melville is ephedrine and pitressin: ephedrine, 0.05 gm. ( $\frac{3}{4}$  grain) and pitressin, 5 units. He gives the patient half this dose. If the blood pressure then drops, an intravenous dose of 0.19 cc. (3 minims) of the mixture usually effectively elevates the blood pressure. Neosynephrin in a 1 per cent solution may also be used. The dose is  $\frac{1}{4}$  to  $\frac{1}{2}$  cc. intramuscularly, or if there is a severe drop in the blood pressure, 0.12 or 0.19 cc. (2 or 3 minims), intravenously, is effective. If used intravenously, the effect is short and may be sustained by the same dose given intramuscularly. An effective method is to mix  $1\frac{1}{2}$  cc. of a 1 per cent solution of neosynephrin in 1 liter of 5 per cent glucose in distilled water. An intravenous drip at the rate of 30 to 40 drops a minute is used. This will sustain a steady level of blood pressure during the operation. The flow can be easily regulated if the pressure drops or returns to normal. The intravenous flow may be maintained after the patient is returned to the ward for a period of from four to six hours. This will maintain a level blood pressure until the effects of the spinal anesthetic have worn off.<sup>3</sup>

## Anuria

Anuria resulting from pathological changes which interfere with renal secretion is not likely to be confused with that due to obstruction.

### Etiological Classification of Anuria

TABLE I

- I. Obstruction:
  - Postrenal:
    - A. Calculus:
      1. In both kidneys.
      2. In solitary kidney.
      3. In only functioning kidney.
      4. In both ureters.
      5. In bladder.
      6. In urethra.
    - B. Ureteral stricture, including post-irradiation type.
    - C. Urethral stricture.
    - D. Block by sulfonamide concretions.
    - E. Occlusion by carcinoma of prostate, bladder, uterus, rectum, etc.
    - F. Extrinsic pressure by abdominal neoplasm, ovarian cyst, etc.
    - G. Surgical injury to ureter or bladder; ligation of ureter.
    - H. Infarct, thrombus, or embolus of main renal vessels.
- II. Parenchymal pathologic changes interfering with secretion:
  - Renal:
    - A. Infectious or inflammatory nephritis; acute pyelonephritis; glomerular nephritis, etc.
    - B. Degenerative or toxic nephroses (Pb, Bi, As and Hg poisoning).
    - C. Severe trauma to kidney, including x-ray.
    - D. Renal changes in eclampsia.
    - E. Renal changes due to incompatible blood transfusions, burns, certain fevers, hyperpyrexia therapy, etc.

TABLE II

- I. Changes outside urinary system:
  - Prerenal:
    - A. Intestinal obstruction or perforation.
    - B. Peritonitis.
    - C. Endocrine disorders (pituitary, thyroid, adrenal, etc.).
    - D. Irradiation sickness.

- E. Pancreatitis; operations on liver, biliary tract, intestinal tract, central nervous system, and brain.
- F. Low fluid intake.
- G. Loss of body fluids by persistent emesis, diarrhea, sweating.
- H. Circulatory failure.

### II. Reflex:

- A. Hysteria.
- B. Surgical trauma:
  1. Operative interventions of all types.
  2. Instrumentation (passage of sounds, ureteral catheters, cystoscopy, etc.).
- C. Reflex anuria in healthy upper urinary tract; opposite tract contains calculus.

### III. Any combination of above types.

The treatment varies due to the type of anuria. Careful kidney function tests, atraumatic handling of tissue, prevention of excessive blood loss, maintenance of adequate blood pressure, copious administration of fluids, and intravenous glucose before, during, and after operation is necessary. *Glucose, sucrose, or dextrose* given intravenously along with forced fluids is very effective. The glucose must be given in high concentrations of from 10 to 50 per cent. In the cardiac risk patient, more concentrated solutions in smaller volumes are indicated. When fluids are not tolerated by mouth, *physiological salt solution* is administered by hypodermoclysis, 4000 to 6000 cc. a day, by vein, duodenal, or rectal tube. Fluids must be forced for weeks after diuresis has been established. Drugs and other diuretic agents are of questionable help. *Potassium nitrate, magnesium sulfate, ammonium chloride, methenamine, pilocarpine, diuretin*, and the *mercury preparations*, although of some use in modifying moderate degrees of oliguria, are of little aid in overcoming total anuria. The hydrogen ion concentration of the blood

and urine should be kept decidedly alkaline; this is accomplished by copious administration of *sodium bicarbonate* and glucose by vein and is maintained by sodium bicarbonate by mouth. Pelvic lavage with various solutions such as warm sodium bicarbonate or *silver nitrate* is a simple, effective method which sometimes aids in stimulating renal secretion.

In the obstructive, postrenal type of anuria, the ureteral calculus obstructing the solitary kidney must be removed. One should not hesitate to do nephrostomy, pyelostomy, or ureterostomy if the condition of the patient does not warrant immediate attack upon the stone. Decapsulation for the relief of nephritis due to toxic poisoning by heavy metals, eclampsia, etc., has fallen into disfavor. In cases of unilateral obstruction presenting reflex anuria on the opposite side, removal of the stone must be followed by the various methods of treating secretory anuria in order to provide relief. The sulfonamides quite frequently are the cause of crystals and this should be constantly kept in mind during administration for other conditions.<sup>4</sup>

### Carcinoma

The treatment of carcinoma of the bladder by *radium* and *x-ray*, both transurethrally and transvesically, has proven to be a very valuable method of procedure.

Wayman and Marting<sup>5</sup> describe a new method of interstitial irradiation for bladder tumors. They do careful bimanual examination under spinal anesthesia, together with a careful cystoscopic study. If the tumor can be palpated *per rectum* or *vaginam*, a transvaginal or perineal extravesical approach to the tumor is undertaken. If the tumor is above the trigone, the bladder is approached suprapubically but is not opened. By means

of a balloon in the bladder, which can be filled or emptied to assist in mobilization of the bladder, adequate exposure of the site of the tumor is made possible. Whatever the approach, radium needles are inserted into the tumor approximately 1 cm. apart and the strings attached to the needles are led out through the incision. A urethral catheter is placed to drain the bladder in such a fashion that the bladder is always partially filled to prevent irradiation of the normal bladder. The other tissues are protected by vaseline gauze packs inserted at the time of the operation. The duration of irradiation is determined by the size of the tumor and the number of milligrams of radium used. The total dose is usually from 10 to 15 threshold erythema doses. Removal of the gauze packs and radium needles is accomplished without difficulty.

### Endometriosis

Endometriosis is usually seen first by the gynecologist; however, it is not as rare a complication in urology as is sometimes thought. There are creeping into the literature more and more reports of endometriosis involving the urinary bladder, and the urologist must be constantly alert to the entity.

During the past year the author has seen two cases of the disease. It is principally characterized by painless hematuria during the menstrual period. The lesion is easily recognized cystoscopically, and the history of bleeding during the menstrual cycle is almost diagnostic.

Kretschmer<sup>6</sup> reports an interesting case in which a suprapubic cystotomy was done. Following panhysterectomy, the patient recovered.

The unfortunate part about the disease is that it is not confined to any particular age group. It must be differentiated from malignant tumors of the bladder. This condition must be sus-



pected where there is a lesion of dusky blue cystic appearance showing what appears to be clots under the surface of the mucosa, with bleeding during the menstrual cycle. It is preferable to take a biopsy through the cystoscope for examination. It must also be remembered that carcinoma and endometriosis may be present and still be independent of each other.

Endometriosis may also involve the ureter. O'Connor and Greenhill<sup>7</sup> stated that cystoscopic biopsy of these tumors has been reported in only a few instances and only on five occasions was the diagnosis satisfactorily made by microscopic study.

The treatment of the disease is *removal* of the *ovaries* or arrest of their function by natural or artificial means. This usually causes an abrupt ending of the disease, but there are some cases on record where ovariectomy has not arrested the condition. *Roentgen irradiation* of the ovaries may be followed by a cure, although the complete removal of the ovary surgically is the treatment of choice. In some cases large doses of *androgen* have been helpful in causing local tumor regression while awaiting the natural menopausal changes which theoretically at least should prove of value.

### Enuresis

Winsbury-White<sup>8</sup> discusses the subject of enuresis from the standpoint of treatment, eliminating as causes nervous disorders, epilepsy, and mental deficiencies. Gross lesions of the urinary tract affect the condition. There is a great deal of work to be done yet concerning the relationship of inflammatory lesions at the bladder neck as causes of the condition, although nonspecific infections in children and adolescents are very common. It is important to ascertain if day frequency accompanies the

condition. In young children, the cystoscope gives evidence in great numbers of patients of bladder inflammation, while in the older children such inflammations are limited chiefly to the verumontanum. He lays great stress on the importance, as a cause, of a tight, pinpoint meatus and on a tight urethra. All of these patients should have excretory urography to rule out chronic changes in the upper urinary tract. Mild dilatations above the constricted point usually precede obstructive findings and these tend to persist after the obstructions are corrected. Residual urine is a very important observation and the average physician does not take cognizance of this important fact in young people. Another important factor in the study of these cases is the fact that uninfected, clear urine can be voided even in the presence of inflammatory changes.

The treatment of this condition demands a full urological investigation, and where tight urethras exist they should be dilated at least once a month for some time. This is not indicated where there is no urethral pathology present. The treatment should not be given during a flareup of frequency or any local inflammation or while catarrhal conditions of the respiratory or alimentary tract exist.

He divides forty patients with enuresis, whom he has studied, into the following classifications:

1. In males due to a small external urethral orifice.
2. In females with a narrow, tight urethra.
3. Such a condition continuing into adult life.
4. Such a condition commencing in adult life.
5. Where local changes are found in later life after the enuresis has stopped.
6. Enuresis with residual urine present.
7. Enuresis with various other types of pathology in both the lower and upper urinary tract.

## Neurogenic Bladder

The experiences of Army surgeons in dealing with partially and completely paralyzed bladders as a result of complete and partial transverse lesions of the cord due to injuries and gunshot wounds will be of invaluable aid and assistance to the civilian physician. Much has been learned about the innervation of the bladder and the proper method of handling these trying cases. One of the most important lessons that has been learned is that if suprapubic drainage is instituted, the suprapubic tube must be placed high in the fundus of the bladder and must emerge from the abdominal wound well above the symphysis pubis. Most of these cases are severely infected from either catheter or suprapubic drainage. The suprapubic wound heals with great difficulty if the suprapubic tube rides close to the symphysis. Great difficulty has been encountered in getting some of these low suprapubic fistulas to heal. The second important factor has been the judicious use of the various urinary antiseptics to prevent urogenital infection in these cord bladders. The *sulfa drugs* and *penicillin* have been of great help. Many of these cases, when they are on catheter or suprapubic drainage, develop calculi in the bladder, ureter, and pelves of the kidney. Most of the stones formed are either of phosphatic or calcium origin. It is essential in many of these cases to keep the urine as acid as possible and to use either aseptic or antiseptic precautions to prevent their formation. If they form, surgery is indicated with the removal of the stone and the proper drainage to that portion of the urinary tract where the stone has formed.

Excluding *tabes dorsalis*, the type of bladder that results from true lesions of the spinal cord will have three com-

mon characteristics: (1) Hypertonicity; (2) inability to empty its contents completely resulting in residual urine; and (3) urinary incontinence. These true cord bladders due to injury show a hypertonic and hypertrophied detrusor muscle, to some degree the bladder is trabeculated, residual urine is present, and there is generally active urinary incontinence. In theory, there is hyperplasia to the portion of the detrusor muscle around the vesical neck. It is believed that the best way to treat these cases is by *transurethral resection*. This technic of transurethral resection has been emphasized by Emmett<sup>9</sup> and Thompson, of the Mayo Clinic. The latter has been doing transurethral resection of the vesical neck in all of these cases of partial and complete transverse lesions of the cord, with a so-called cord bladder resulting. He is thoroughly pleased with his results and he recommends this treatment in these cases. Transurethral resection of the vesical neck is not indicated perhaps in the cord bladder of syphilis and other infectious diseases of the cord.

In discussing urinary control in neurogenic bladders, VanDuzen<sup>10</sup> does presacral neurectomies and when little benefit is derived from this procedure, he has performed gracilis muscle transplants, and, as he says, with mediocre results. He believes that the uninhibited neurogenic bladder may be relieved by *ephedrine sulfate* or *methyle testosterone*, and believes that some of these cases are improved by presacral nerve resection.

The so-called automatic bladder is discussed by Hanlon.<sup>11</sup> He condemns intermittent catheterization and thinks that overdistention and overflow incontinence are to be avoided. He recommends presacral sympathectomy. In discussing this problem, Lewis says that the development of an automatic bladder de-

depends upon the number of reflex arcs intact and that lesions below the level of D-12 divide either the motor or sensory or both sides of the reflex arc. He believes that cystometric studies are indicated, not for diagnostic purposes, but to complete and augment the neurological survey.

Others have treated the condition by clearing up the infection and training the patient to develop an automatic bladder by limiting the quantity of fluids taken during certain hours and expelling the urine with a light pressure to the abdomen at regular time periods so that the training in the habit of emptying the bladder at certain periods, with certain quantities of fluid, may be developed.

The treatment of incrustations of the urinary tract, particularly those due to alkaline infections, has been greatly improved in the past few years by continuous irrigations with solutions G and M. The formula for solution G is:

Citric acid (monohydrus)....	32.3 gm.
Magn. oxide (anhydrous).....	3.8 gm.
Sod. carb. (anhydrous) .....	4.4 gm.
Distilled water .....	ad 1000.0 gm.

Solution M is made by substituting malic acid for the citric acid.

These solutions are definitely bactericidal against strains of *B. coli*, *B. proteus*, *B. morganii*, and *Strept. faecalis*.

There are several types of cases where an incrustated cystitis develops and these are very difficult to cure. Quite frequently, an incrustated cystitis results from late radium ulcerations of the bladder following the treatment of carcinoma of the bladder. The method of administering solution G or M in a situation of this kind is to take an indwelling three-way Foley-Alcock catheter and administer the solution by means of a Murphy drip at a rate of from 40 to 60 drops per minute. Continuous drainage is thus accomplished along with tidal drainage

and periodical distention of the bladder with solution G. The patient's fluid intake should be held at a level of about 3000 cc. during the twenty-four-hour period that solution G is being used.

The investigations of Herger and Sauer<sup>12</sup> show that solution G is definitely useful in dissolving certain types of stones in the bladder without any ill effects to the patient. Their most impressive results were in those patients with incrustated alkaline cystitis and incrustated radium necrosis. The majority of their patients were virtually cured in a treatment lasting from two to four weeks. In some cases it has been found necessary to repeat the treatment. In surgical removal of stones from badly infected kidneys, nephrostomy should be done routinely in order to facilitate post-operative irrigation treatment with solution G.

In the writer's experience, this has proven to be a very efficacious manner in which to clear up infections in the pelvis of the kidney and to eliminate sandy concretions that may form after the stone has been removed.

Lins,<sup>13</sup> a native of Brazil, was interested in a treatment which the Indians of the Amazon Basin used to dissolve the skeletons of a small fish which invades the urethra and bladder of river bathers. The native medication which was used was made from the astringent juice of the buitach apple. As a result of the experiences of these natives, Lins developed a synthetic formula for the solution which consists of the following:

The synthetic formula has a pH of 4.0.

Methanamine .....	10.0 gm.
Proteolytic enzymes (pepsin)...	1.0 gm.
Citric acid .....	32.0 gm.
Tannic acid .....	32.0 gm.
Magnesium oxide .....	4.0 gm.
Sodium carbonate .....	4.0 gm.
Water .....	1000.0 cc.

He has treated twelve patients at the Brady Urological Clinic in New York City for those conditions where solution G has been used by other writers. The solution is administered per rectum rather than directly into the bladder in cases of incrustrated alkaline cystitis. A Foley bag catheter was placed in the rectum and the solution, at 98.6° F., was administered by means of an intravenous clysis outfit at a rate of 12 drops per minute. Approximately 3000 cc. of solution was used daily. Cystoscopic examinations were usually made at weekly intervals for the purpose of determining whether or not continuation of treatment was indicated. Depending on the response to treatment, instillations were carried out for periods ranging from one to three weeks. Irrigations of the rectum with the solution were well tolerated in all the patients.

**Aluminum hydroxide** in doses of 20 gm. was also administered two or three times a day so that the phosphorus was retained by the intestine.

In all of these twelve patients with incrustrated ulcerations of the bladder and alkaline cystitis, the response to treatment was satisfactory.

It is the author's impression that this treatment is of value not only in urinary tract infections which are complicated by the formation of alkaline incrustations but may be used also as a stone-dissolving agent.

### Urinary Bilharziasis

Following this war, where many of our service men and women have been in the South Pacific and other tropical countries, there will be many vague conditions develop which will require our attention. Many tropical diseases directly affect the urinary tract and one of the most important of these is schistosomiasis.

A short time ago, while visiting at Walter Reed Hospital, it was the writer's privilege to see several cases of this disease. Once having seen them, they are not readily forgotten.

The symptoms are vague. They consist of headaches, backaches, fever, and the only urinary symptom is usually frequency. The physical examination, including laboratory findings, is usually negative except for an eosinophilia. The disease is diagnosed by cystoscopy, examination of the urine, and biopsy. The lesion in the bladder can be confused with a papilloma but more often it suggests an inflammatory condition. Around these inflammatory areas are yellow gray, tiny nodular masses. Cultures of the urine before rupture of these masses are usually sterile. Tissue should be taken from them for biopsy. Following biopsy, the urine should be centrifuged and *Schistosoma hematobium* ova are easily found. The organisms producing the disease are blood flukes. Their home is, primarily, in the vesical venous plexus of man. The fertilized ova are deposited in the small submucous veins of the urinary bladder. These eggs erode the wall of the venule and drop into the bladder cavity and are voided. The larva then must be consumed by the fresh water snail and they live in the snail's liver. They are then released from the snail's body into the water where they must find a human host within forty-eight hours in order to survive. They enter the human host usually through the skin. Entering the blood vessels, they mature in the human liver. At maturity, they migrate to the vesical venous plexus where mating and egg laying occur. The disease is endemic in Africa, the islands of Madagascar, Mauritius, Reunion, the southern fringes of Portugal and Greece, and many other places. It

is also known to occur in some of the areas of the South Pacific.

At the present time, the diagnosis in the human must await the symptoms and findings of the disease in the urinary bladder. The treatment consists of giving *trivalent sodium antimony salt*, known as fuadin. This is given intramuscularly in total dosage of 40 cc. over a period of sixteen days. Fuadin contains 13.5 per cent of antimony and is marketed in a clear, isotonic solution for intramuscular use. Each 1 cc. of the solution represents 8.5 mg. of trivalent antimony. It is excreted principally through the urine and slightly in the feces. Theoretically, its values over *tartar emetic* are that it is given intramuscularly, is less toxic, and requires smaller doses with consequent less antimony necessary to produce a cure.

During the course of treatment, the patient will notice a large amount of flaky material passing with the urine. Examination of the urine will show that it is heavily loaded with ova and bladder epithelium. In approximately ten days, the bladder picture shows marked improvement and no ova can be demonstrated in the urine. It is better to discontinue the drug for thirty days and repeat a full course of the drug over another sixteen days. The patient then should be rechecked every three months for an indefinite period of time.<sup>14</sup>

### Treatment of Urinary Frequency in Women

Frequency of urination in women is a symptom that demands treatment. It may be the only symptom and calls for a complete conventional urological study and a diagnosis. These conditions must not be considered as of nervous origin but should be completely investigated. Inspection and examination of the pelvis should be routine. Not infrequently, a

part of the urethral mucosa crowding into the lumen of the urethra or out through the urethral orifice will be found. A caruncle may be found. Tissue of this kind should be biopsied. The urethral canal should be palpated through the anterior wall of the vagina and any expressions of pus should be smeared. The urethra in the female is subject to infection. Catheterized specimens of urine should be studied and cultured. The *sulfa drugs* and *penicillin* should not be administered until a complete urological survey has been made, the source of the infection ascertained or the mechanical cause of the bladder neck irritability diagnosed, and proper treatment instituted to correct the condition.

Granular urethritis is a condition that is not given its proper place as a definite disease entity. Strictures of the female urethra are not uncommon. As a matter of fact, granular urethritis, with or without decreasing the caliber of the female urethra, is the cause of frequency and urgency of urination in a very large percentage of cases. Simple *dilatation* of the urethra with *cauterization* of the granulation tissue in the urethra, as a rule, will result in complete relief.

In cases of tuberculous cystitis, the bladder is extremely irritated, with small capacity. Quite frequently, this condition is aided by the use of *tincture of hyoscyamus* and *potassium citrate*. The dose of tincture of hyoscyamus is between 20 and 30 drops with 0.98 gm. (15 grains) of potassium citrate. Tincture of opium, 10 to 20 drops every three or four hours, may be of value. If these simple things do not help in the tuberculous cystitis, lavaging the bladder with 1:10,000 *silver nitrate solution* is of value and the instillation of 1 ounce of *gomenol* or *oil of cajuput* in a 2 per cent solution of olive oil has been helpful. Some men even

recommend lavaging the bladder with a 0.9 solution of *sodium acetyl sulfanilamide*, instilling 1 ounce into the bladder and repeating this treatment twice weekly.<sup>15</sup>

### Genitourinary Tuberculosis

Two hundred and ninety-three cases of genitourinary tuberculosis were carefully studied by Davis<sup>16</sup> with the following pertinent observations:

1. Clinically, about 35 per cent of renal tuberculosis is bilateral.

2. Among 221 male patients, there were 126 cases of epididymitis (57 per cent), of which more than one third were bilateral. Renal tuberculosis was ruled out in eleven cases. The prostate gland is frequently involved, even though it feels normal by rectal examination.

3. Only 42 (14 per cent) cases of renal tuberculosis showed evidence of severe cystitis, and as many as 137 (47 per cent) complained of no bladder symptoms at all.

4. Twenty-two per cent of all orthopedic cases have had genitourinary tuberculosis. Of the 293 cases, 107 had skeletal lesions.

5. One hundred and thirty-three cases of this series had active pulmonary tuberculosis.

6. There were seventeen cases of tuberculous meningitis, and eleven cases of acute miliary tuberculosis.

7. There were 121 deaths in this series (41 per cent). These may be classified as follows: 27 per cent among those whose disease was primarily renal; 36 per cent in the skeletal group; and 65 per cent in those whose major disease was pulmonary.

Figures like these make the management of the case of genitourinary tuberculosis one of constant observation. There are, as indicated, few cases in which there is no involvement of other anatom-

ical structures and often the diagnosis and treatment of the urological condition are insufficient to return the patient to normal life. A patient with urinary tuberculosis is still a tuberculous patient, and with the clinical improvement of the urological condition, regardless of the clinical result, these patients should all be referred to a competent expert on general tuberculosis, and the patient's life from there on should be based on a constructively managed general tuberculosis regime.

### Gonorrhea

So much has been written during the past few years on sulfa and penicillin and their use in the treatment of venereal disease that it is time to take stock of the various reports that have been issued and evaluate the therapy. Miraculous reports were submitted as to both sulfa and penicillin by the early investigators, particularly in the treatment of venereal disease in the Army. Certain strains of the gonococcus were found to be sulfa-resistant; certain strains were found to be resistant to penicillin, and certain strains that were resistant to each separately seemed to be vulnerable to the combination of both drugs. It was soon found that in the pathological lesions of the lower urinary tract these drugs were only adjuncts in the treatment of the disease and that certain surgical measures and local therapy were still necessary to consider the patient cured.

The drawback in the use of many of the various *sulfonamides* was the danger of anuria and renal damage if the drug was continued for long periods of time and if the use of alkalinizing agents was eliminated from the treatment. Also, a distinct danger arose from the indiscriminate use of the sulfonamides by the patient without medical jurisdiction. The

sulfonamides should never be given except under medical supervision. A keen watch should be kept for evidence of renal damage and dysfunction.

The rôle of *penicillin* in the treatment of gonorrhea was first studied in those cases that were sulfonamide resistant. Later, penicillin was substituted for the sulfonamides in the treatment of large groups of these patients, particularly those in the Service. The drug was administered in two ways: First, it was discovered that 100,000 units administered in doses of 10,000 to 20,000 units every three to six hours would cure the average acute infection; then, later, 100,000 to 300,000 units in a single dose in beeswax and peanut oil gave equally brilliant results. Penicillin will cure most cases of acute gonorrhea but one course of treatment may not be sufficient. It may have to be combined with pyrotherapy and the sulfonamides. Longer periods of observation are advocated in these patients. They should be treated with *sulfa* and *penicillin* separately or in combination. These patients may be clinically cured but may become carriers unaware of their infectiousness to others. The absence of clinical symptoms is not sufficient proof of cure.

Studies have been made which show that 100,000 units is not as efficacious as 200,000 units in the treatment of the disease. In 485 patients who were treated by an initial course of 200,000 units of penicillin, failures were determined by positive cultures during the period of hospitalization. Two patients in this group had positive cultures, although both had no clinical symptoms and both denied sexual intercourse. Approximately 34 of the total number in this group failed to respond to treatment. The passage of a provocative sound after clinical cure will lead to the find-

ings of some of these failures. In 30 of the 34 failures, a second course of 200,000 units of penicillin was given. Twenty-four of these cases fulfilled the minimum criterion of cure. Of these, 6 were still infected. The failures were retreated with a third course of 200,000 units of penicillin. Four were cured with penicillin alone, 1 was cured with penicillin and sulfadiazine, and 1 failed. This last case was treated with a fourth course of 200,000 units of penicillin with typhoid pyrotherapy and failed. A fifth course of 200,000 units of penicillin with sulfathiazole and artificial pyrotherapy produced the cure. These results emphasize the necessity for a long observation period after therapy.

It is possible that walled-off organisms in the prostate, in cervical and urethral foci may not be affected by the treatment and that these areas may later break down and produce a recurrence or a carrier.

There has been some criticism about the passage of sounds in the presence of penicillin-treated acute gonorrhea, but in over 700 patients no complications have resulted from this procedure. The sounds are passed within the first twenty-four hours following the completion of the penicillin therapy.

A case should not be considered as cured until there have been three consecutive negative cultures over a four-week observation period. If this type of observation is not practicable, three cultures over a one-week period is recommended. It is desirable to maintain the patient on a three months' observation period during which time the patient has had a minimum of six consecutive negative cultures.

It is suggested that penicillin in 200,000 units be administered at two-hour intervals. Patients treated in the hospital and those treated as outpatients

have about the same failure rate. It is very important to remember that penicillin therapy may produce a carrier state and increases the spread of the disease.<sup>17</sup>

### Kidney-Calcium Urolithiasis

Calcium urolithiasis occurs where there is hypercalcinuria, urinary tract infection, and urinary tract stasis. There is much initial precipitation of calcium phosphate which results in the formation of many small calculi in those patients who are bedridden for any length of time and who have stasis. This is particularly true in patients who have had fracture of the spine, of the pelvis, of the femur, traumatic strictures of the urethra, or other conditions which require them to be hospitalized or in bed for any great length of time. All of these patients should have frequent x-ray checkup examinations to spot the beginning of calcium urolithiasis. Hypercalcinuria cannot be prevented in the bed patient; but dilution of the urine by maintaining a large urinary output is of value. Stasis cannot be avoided when there is some central nervous system damage and infection is almost impossible to prevent where catheters or drainage tubes are necessary for urinary tract drainage.

#### Conditions Predisposing to Calcium Urolithiasis

1. Disease producing prolonged immobilization of the body :
  - a. Fractures of the spine or extremities associated with prolonged immobilization of large bones.
  - b. Chronic osteomyelitis.
  - c. Chronic arthritis, or other bone joint disease producing immobilization of large portions of the skeleton.
  - d. Neurologic damage as a result of trauma or disease producing prolonged immobilization.
  - e. Chronic visceral disease requiring prolonged recumbency.

2. Changes in the urinary organs :
  - a. Congenital anomalies associated with stasis.
  - b. Acquired obstructions, stricture of urethra, etc.
  - c. Paralysis of urinary passageway.
  - d. Introduction of infection into urinary tract.
  - e. Foreign body in urinary passageway.
3. Endocrinopathies :
  - a. Hyperparathyroidism.
  - b. Hyperthyroidism(?)\*
  - c. Hyperpituitary disease(?)
4. Focus of infection elsewhere in body(?).
5. Vitamin deficiency or excess :
  - a. Vitamin A deficiency(?).
  - b. Vitamin D excess.
6. Metabolic abnormalities :
  - a. Idiopathic hypercalcinuria.
  - b. Changes in colloids(?).

Conditions and situations predisposing to calcium urolithiasis are: (1) The maintenance of a large fluid output; (2) the control of diet; (3) the control of stasis; (4) the control of infection; (5) the continuation of treatment for three months after immobilization has ceased, and (6) frequent roentgenographic checkup examinations.

The method used by Flocks<sup>18</sup> for x-ray examination of these patients consists of taking a plain film and a second film twenty minutes after the intravenous injection of 20 cc. of diodrast. This is done one month after the onset of the predisposing condition and then one month, two months, three months, and every six months for one year after the onset of the predisposing condition.

### Kidney Injuries

In all serious injuries, whether in peace or in war, it is necessary to get the patient to void as soon as possible because the only important telltale sign of urinary tract injury is usually hema-

\* Conditions with question mark are put in mainly upon a theoretical basis. Others are put in upon clinical basis.



turia. With pelvic injuries, extravasating urine may pour into the tissues for hours before a bladder rupture is even suspected. Once injury is surmised, it is imperative that its extent and severity be known. From a clinical point of view, patients with renal injury should be put to bed and watched carefully. While the occasional case will require surgical intervention, the majority will get well without it. An operation performed in the event of a ruptured kidney usually must be done in the presence of substantial shock and is commonly associated with other severe injuries, while a bruised or ruptured kidney, providing the hemorrhage is not too severe, will repair itself without surgical intervention. Signs of progressive bleeding must be watched for in suspected rupture of the kidney. Every patient with severe body injury should be made to void or be catheterized as one of the very first steps in the examination. A ruptured bladder demands immediate suprapubic cystostomy, as does a ruptured urethra. Splinting the ruptured urethra on a catheter, with suprapubic cystostomy, should be done as soon as the diagnosis is made.<sup>19</sup>

### Wilms' Tumor

The most common kidney tumor in early life is the so-called Wilms' tumor, which is an adenomyosarcoma or embryonal mixed tumor of the kidney. The majority of these tumors occur in children but occasionally one is encountered in the adult.

The diagnosis depends upon the clinical history, physical signs, especially a palpable mass in the abdomen, x-ray examination of the chest, as well as urological studies of the urinary tract. Usually the tumor is the first thing that is discovered, the mother noticing the increased size of the abdomen while she

is bathing the child. By this time, the tumor is already incurable and the patient will, in the majority of the cases, die of his disease.

The differential diagnosis is between adrenal tumor, congenital anomalies of the kidneys, retroperitoneal sarcoma, mesenteric cyst, omental cyst, enlargement of the spleen and liver, and ovarian cyst. Occasionally, the first symptom will be painless hematuria. Unfortunately, bleeding is usually a very late symptom and the tumor is usually beyond the cure stage when this occurs. As a rule, the diagnosis is easily confirmed by urological roentgenological examination. The treatment of the disease has been unsatisfactory and usually the patient is inoperable when first seen. There is considerable controversy between the different authorities concerning pre- and postoperative irradiation as an adjunct to surgery in the treatment of the disease. Giles<sup>20</sup> combines preoperative therapy with nephrectomy, followed by postoperative irradiation. There are few cases of Wilms' tumor reported with a five-year cure.

A large series of cases has been reported by Ladd, White, and others.<sup>21</sup> They feel that *nephrectomy* alone has given just as good results as where preoperative *irradiation* therapy has been employed with nephrectomy.

### Pyelitis of Pregnancy

Many reasons have been given to explain the dilatation. Increased intra-abdominal pressure, compression of the ureter by the presenting parts, and pressure produced by the growing pregnant uterus are commonly used explanations. Some are satisfied by ascribing the dilatation to the hormones which at the same time produce the usual changes peculiar to pregnancy, the enlargement of the breasts, the softening of the pelvic

structures, and the enlargement of the vaginal tract. What the purpose and use of the dilatation of the urinary tract and increased bladder capacity, if due to hormonal action, are not clear. However, stasis of urine in the ureter and kidney pelvis results, and, whenever stasis in the body occurs, infection may result if the caustive organisms are introduced.<sup>22</sup>

### Tuberculosis

*Promin*, one of the sulfone group of drugs, has been used recently in the treatment of experimental and clinical tuberculosis. Some workers have reported favorable effects in tuberculosis in guinea pigs, but in none of these cases was the disease eradicated. The encouraging results which were reported by Steeken, Heise, Feldman, and others caused Wang and Gonzalez-Iman<sup>23</sup> to use the drug in the treatment of genitourinary tuberculosis.

They used an initial dose of 0.2 gm. daily for a week or ten days until the patient's tolerance was determined and then gradually increased it to 0.6 to 0.8 gm. daily. The administration was continued over a sufficiently long period of time to permit some evaluation of the effect. Four patients with active renal tuberculosis were selected, all of whom had acid-fast bacilluria. Of these four patients, only one considered that his symptoms were improved. The *promin* was administered together with all the other conventional methods of treatment. The results of the treatment, however, were anything but satisfactory and the authors feel that a much longer experimental study of the drug must be had before it can be considered of any value in the treatment of genitourinary tuberculosis.

### Male Climacteric

Much has been written pro and con concerning the male climacteric. That

there is such a period in the life of the male is undisputed.

In a study of fifty-four male patients during this particular period, one of the types of testicular hypofunction or afunction is considered the etiological factor in producing the hypogonadal or climacteric syndrome. The symptoms, similar to those of the female, as a rule are much milder and not so apt to be taken into consideration in the care and treatment of men in this period of life.

*Testosterone propionate*, given intramuscularly, 25 mg. three times a week, has caused a marked diminution in this hypogonadal period and produces a distinct sense of well-being. The most important symptom of this period is the mental depression that goes with it, and this seems to be completely relieved by this form of therapy. The treatment should be kept up for a considerable period of time after the relief of the symptoms has been accomplished. The drug may be given orally, by inunction, and by implantation. When given orally, from three to eight times as much of the drug must be used as is used if given by intramuscular injection. Inunction is not satisfactory and implantation allows for no symptomatic control of the dosage of the drug. It should never be used to stimulate the impotent, nor should any promises be made that there will be a return of potency. Such promises or such hope may prove disastrous to the patient.

Most males pass through this period without much discomfort; others have a three to six months' disturbance of equilibrium, while others, without knowing the cause of their trouble, pass through a three- to five-year period of disturbance. Many of these patients will often be greatly benefited by the cooperation of the neuropsychiatrist and the urologist.<sup>24</sup>

### Prostate

**Thrombin as an Aid in Prostatic Surgery**—Recently, Dr. Smith and his associates at the University of Iowa have described a very powerful preparation of thrombin. This substance is readily soluble in water or normal saline solution. It is slightly opalescent and has a  $pH$  of 7.2, retaining its activity for several days if kept refrigerated. The substance is nontoxic when applied to tissue surfaces. It has been used to control bleeding after section of the liver and brain in experimental animals. O'Connor<sup>25</sup> has used the substance as a hemostatic aid following transurethral prostatectomy.

The solution is prepared by dissolving the thrombin in 10 cc. of sterile normal saline just before using it. The solution is then injected through the catheter following transurethral resection of the prostate. They have used it in 140 consecutive cases following transurethral resection. Their technic is as follows:

When the tissue resection has been completed, the resected area is carefully inspected for obvious "spurting" points and these areas are coagulated at the point of hemorrhage. A diffuse oozing frequently continues when careful visualization fails to show a definite point of hemorrhage. When individual bleeding points have been recognized and coagulated, even though a diffuse oozing continues, the resectoscope is withdrawn and a No. 22 or 24 Foley bag catheter is inserted. The bladder is then repeatedly lavaged with sterile water until the return flow is as clear as it will apparently become after a period of several minutes. Ten cubic centimeters of thrombin solution is then injected very slowly through the catheter and the catheter lumen is closed. After an interval of several minutes, the catheter bag is then inflated to the desired extent and gently drawn down into the prostatic cavity. The patient is returned to bed with the catheter closed and a period of 30 to 60 minutes allowed to elapse before the catheter is opened and connected to the tubing which is attached to a bottle at the

side of the patient's bed. The original drainage from the catheter is of a coal black or inky color but drainage is usually free and uninterrupted. No irrigation of the catheter is practiced at any time unless it is obvious that the patient has continued to bleed into the bladder and the clots are obstructing urine outflow from the catheter. (This condition has occurred in only 5 patients of the 140 in whom this technic has been used.) It must be emphasized that continuous or intermittent irrigation of the catheter will defeat the purpose of thrombin (topical). Since thrombin produces hemostasis by surface clotting rather than by extension of clotting into the vessels, a thin film of surface clot must be retained if successful maintenance of hemostasis is to be accomplished. The conversion of thrombin to fibrin is actually a "flash-reaction," hence continued bleeding suggests:

1. Insufficient amount of thrombin (topical).
2. Hemorrhage from vessels too large to control by this method of hemostasis.
3. Oozing from beneath a well-formed or imperfect clot.
4. Deficiency of other clotting factors, as in certain hemorrhagic entities (fibrinogenopenia).

O'Connor has also used it in a series of 47 suprapubic enucleations of the prostate. In these cases the prostatic cavity is packed with two-inch wide mesh gauze, the initial ten inches of which have been saturated in 10 cc. of the thrombin solution. The pack is removed in forty-eight hours. The patient is given intravenous *sodium pentothal* analgesia, after returning to his bed. This procedure is important as it prevents pain and vesical neck spasm during and immediately after the withdrawal of the pack. Thrombin is considered the most effective surface hemostatic for the control of surface oozing following prostatic surgery. There have been no signs of toxic or dangerous thrombotic sequelae. This is a valuable adjunct in certain cases of postoperative bleeding, although it is questioned whether it is necessary to use it routinely.

### Carcinoma

The diagnosis and treatment of prostatic carcinoma have improved immeasurably during the past few years. The diagnosis of the condition depends upon the skill and judgment of the first physician consulted by the patient. It is always well to keep in mind that men from fifty-five years of age on are in the prostatic age and that no physical examination is complete without a careful rectal examination. A hard, single node in an otherwise normal prostate may be malignant and, if found, should immediately suggest a searching examination. A large percentage of cases of carcinoma of the gland never causes obstructive symptoms and are usually found at autopsy or after bony metastasis has taken place. Experience has proven that these single masses or lumps in an otherwise normal feeling gland must be biopsied. If malignancy is present, the total perineal prostatectomy as advocated by Young is definitely in order. These cases are usually curable if completely operated upon at this time. Once metastasis has taken place, total perineal prostatectomy with or without obstruction is not curative and is probably contraindicated.

About 18 per cent of the benign adenomas or hypertrophied prostates will be found to be undergoing malignant degeneration when first seen. This pathological entity is entirely different from the true prostatic cancer as we ordinarily consider the condition.

The symptoms of prostatic cancer vary with the progress of the disease. Some cases metastasize early, some late. All suspected cases should have x-ray examinations of the chest, pelvis, and spine. Varying disturbances of micturition are noted. In some cases, the obstructing discomfort is very mild; in

others, marked. Pain, as a rule, is a late symptom. Few of these cases bleed until late. Cachexia, loss of weight, appetite, *et cetera*, may be very late symptoms. Given a patient over fifty-five years of age with any history of disturbance to the function of voiding, an immediate demand for a complete urological survey is imperative. Once the diagnosis is made, the treatment immediately falls into several categories. The suspected cancer of the gland demands verification. If no metastasis can be demonstrated, and if the serum acid phosphatase level is normal, the indication is that the disease is still confined within the prostatic capsule. A serum acid phosphatase over 5 is a direct indication of metastasis even though the x-ray doesn't demonstrate the condition.

When metastasis begins to occur (to the bony pelvis, lumbar vertebrae, ribs, lungs, and to the prevertebral chain of lymph nodes) there is pain due to impingement upon the nerves. There is a rise in the serum acid phosphatase (which normally is 1.5 to 3 King and Armstrong units per 100 cc. of blood) to values above 5 units when there is extension of the malignancy beyond the confines of the gland capsule. Removal of the chief source of the androgens usually produces a drop in serum acid phosphatase values, an abrupt decrease in pain, and roentgenological evidence of the disappearance of bony metastases. There is also a shrinkage of the mass of malignant tissue in the prostate, often sufficient to permit the passage of urine with more ease even when no operation has been done on the prostate.

The following is a statement from the Paul-Lewis Laboratories: "*Acid Phosphatase*: Normal values for the acid phosphatase activity of serum when determined by the method described (modified King and Armstrong technic) range

around 3.25 units per 100 cc. of serum. Values falling below 5 units per 100 cc. of serum may be regarded as lying within the normal range. Values between 6 and 10 units per 100 cc. of serum are suspicious of prostatic carcinoma and should be confirmed by further determinations, over an extended period of time if necessary, and supplemented by other diagnostic procedures, cystos-

major obstruction will be relieved. Most important is the study by the pathologist of the tissue removed. The prevalent type of malignancy of the gland is an adenocarcinoma. There is no satisfactory treatment of any other type. If the pathologist reports an adenocarcinoma, the treatment may be divided into three or a combination of three categories. The method of choice for remov-

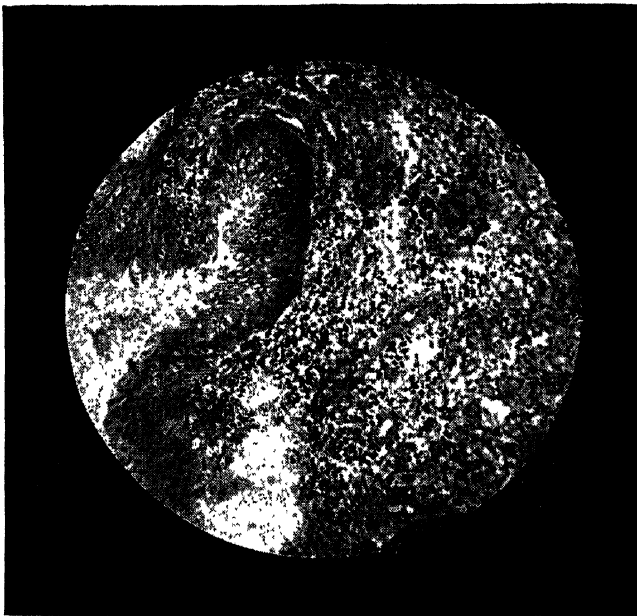


Fig. 1—Benign granulomatous caruncle. A purely benign inflammatory lesion. Note the round-cell infiltration and no evidence of malignancy. (Hess, E.: *Pennsylvania M. J.* 48:1150 (Aug.) 1945.)

copy, biopsy by transurethral or perineal routes, and roentgenologic investigation for skeletal metastases. Values over 10 units per 100 cc. of serum are diagnostic for prostatic carcinoma with metastases."

An advanced carcinoma of the prostate reveals to the examining finger in the rectum a hard, irregular fixed bladder neck and enlargement of the gland. It is usually stony hard and, once felt, is seldom mistaken for any other condition. Even if there is little or no obstruction present, it is important to remove as much of the prostatic tissue as possible, so that a mild as well as a

ing tissue in suspected carcinoma is by **transurethral resection**. Huggins, in his monumental research work upon the disease, has shown that the androgens secreted by the testes are stimulating to the prostatic epithelium. In his work he proved to the satisfaction of most urologists that the removal of the testes caused regression in the growth of the prostatic carcinoma, together with regression of the metastases. Other workers attempted to neutralize the androgens by the free administration of the female sex hormone (the estrogens). Still others attempted to destroy the testes

by deep x-ray therapy. Most observers are satisfied that radium and x-ray directed at the carcinomatous gland itself are worthless.

Many observers do orchiectomy surgically the moment the diagnosis is verified whether or not there is metastasis. Then if the growth begins to recede and the patient's general condition improves, no further treatment is indicated. If,

### Ureter Obstruction

A great many urological conditions seen in adult life can be traced directly to their existence in childhood. There are a great number of these urological abnormalities which are undoubtedly of congenital origin. If many of these lesions were discovered in infancy or childhood, the degree of renal destructive disease found in adult life would be greatly

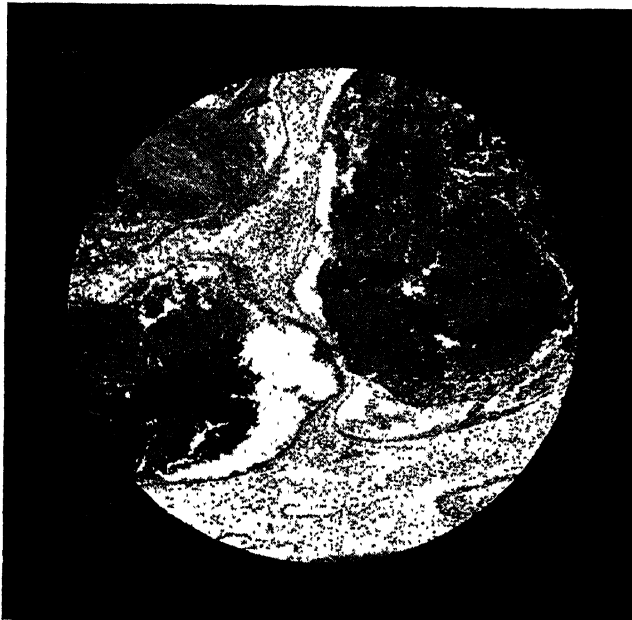


Fig. 2—Benign papillomatous caruncle. Has an occasional cell with a very dark-stained nucleus and an occasional mitotic figure. No round-cell infiltration. This is an epithelial hyperplasia, considered benign, but some pathologists would call the lesion suspicious. (Hess, E.: Pennsylvania M. J. 48:1150 (Aug.) 1945.)

however, there is remission after *orchiectomy*, the female sex hormone is exhibited in large dosage. Five milligrams of *stilbestrol* daily is a favorite. Its effects are better if given hypodermically, but in many cases satisfactory results seem to be obtained if the drug is given by mouth. The use of the drug may be kept up more or less indefinitely unless unsatisfactory side results become evident. The most important side results seem to be a painful hypertrophy of the male breast and various gastrointestinal disturbances.

diminished. It is not infrequent to find that the pyelitis of pregnancy is the reactivation of a childhood pyelitis due to an unrecognized ureteral obstruction which has existed probably since birth. It has also been clearly recognized for years that an albuminuria and pus in the urine is very often caused by an unrecognized asymptomatic ureteral obstruction of congenital origin.

The introduction of excretory urography has simplified the study of the urinary tract in children, and this should be used whenever there is any sugges-

tion that repeated attacks of so-called colitis or gastrointestinal disturbances might be due to some anomaly or infection in the urinary tract. Persistent pus in a child's urine should demand such a study.

Obstructions occur at various places in the urological tract from the pinpoint meatus to the ureteropelvic junction.

Enuresis in children demands at least an excretory urogram. The so-called

operation, in which several parallel vertical incisions are made through the serosa and muscularis with the mucosa left intact; (2) reimplantation of the excised ureter into the pelvis at its most dependent portion; (3) Foley's modification of Schwzer's Y-incision with V-closure; (4) the Fenger technic in which the stenosed region is incised longitudinally with a transverse closure; (5) the operation described by Gibson in 1940.



Fig. 3—Benign angiomatous or telangiectatic caruncle. This is a vascular tumor, benign, and the spaces between the stroma of the tumor are filled with blood, with nothing even suggestive of malignancy. Has a marked clinical appearance of malignancy, however. (Hess, E.: *Pennsylvania M. J.* 48:1150 (Aug.) 1945.)

chronic appendix should certainly be differentiated from ureteral obstruction with hydronephrosis. Ureteropelvic obstruction is not rare but extremely common and many of these children will be obliged to submit to nephrectomy if the condition is not discovered early. When a hydronephrosis is discovered in a child and a stricture of the ureteropelvic junction is demonstrable, palliative surgery is indicated.

Five basic operative technics have been employed: (1) The Rammstedt

He proposed that high insertion of the ureter be corrected by incision of the valvelike partition downward without suture of the cut edges.

If aberrant vessels are found, ligation and division may be safely accomplished in most instances, although occasionally it may be necessary to sever and re-implant the ureter.

The effect of gentle compression of the vessel on the involved portion of the kidney should be determined before ligation is done.

Quinby is of the opinion that the obstructive effects of anomalous vessels may be the result of the pulsation of the artery against the ureter interfering with peristalsis and producing urinary stasis, rather than actual constant encroachment. High ureteral insertion is best managed by the Y-incision or the Gibson technic. In true stricture, the Ramstedt type of procedure obtains the best results. The Fenger repair is em-

relief of the obstruction more than justifies the surgical risk and will quite frequently prevent total destruction of the kidney by infection, calculus, pyonephrosis, and destructive hydronephrosis in adult life.<sup>26</sup>

### Urethra Caruncle

The lesion called caruncle is supposed to be a chronic inflammatory process in the female urethra. Removed caruncles

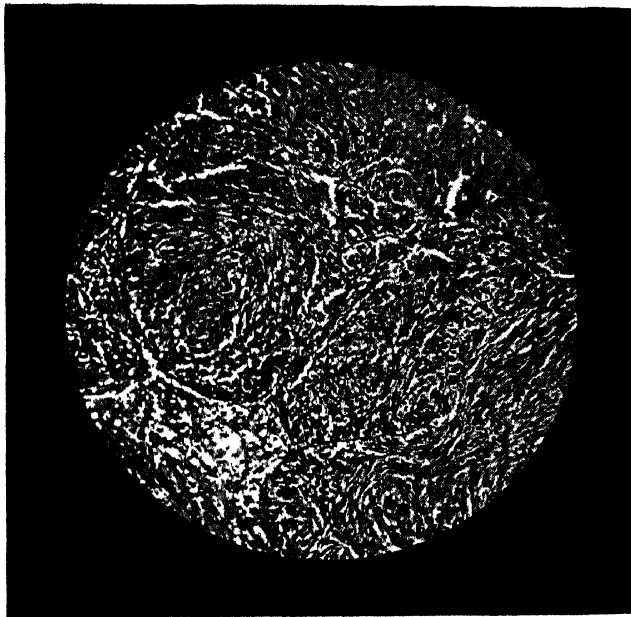


Fig. 4—Early squamous cell carcinoma. This one large group of squamous cell nests was the only evidence of malignancy in an otherwise typical granulomatous urethral caruncle, early malignancy. (Hess, E.: *Pennsylvania M. J.* 48:1150 (Aug.) 1945.)

ployed infrequently. Regardless of the type of procedure, diversion of the urinary stream by a temporary nephrostomy with high fixation of the kidney is advisable.

Splinting of the upper ureter by means of a catheter should also be carried out. If the hydronephrosis is marked, partial resection of the sac may be warranted to facilitate the elimination of stasis and infection.

The results following these conservative operations are good and the restoration of adequate renal function with

examined under the microscope are frequently reported back as malignant. Therefore, it is very important that these lesions be completely removed and as completely examined.

There are three types of chronic inflammatory lesions of the urethra, all of which are classified generally as caruncle. For the purpose of clarification, diagnosis, and treatment, these are:

1. The external caruncle.
2. The internal caruncle.
3. The rosette of proliferative urethral mucosa.



The lesion may be the typical cherry red tumor protruding from the urethra. It may not be visible unless the examiner separates the lips of the urethral meatus, or it may consist simply of swollen, everted, edematous mucosa.

Primarily, the three common subjective symptoms are:

1. Frequency or burning during urination.

cle requires a little more careful observation. The percentage of the latter to the former is approximately fifty-fifty. Heretofore many of us considered these lesions benign and of inflammatory origin; others have diagnosed the lesions as malignant and have destroyed them without benefit of biopsy. Both of these attitudes are unscientific and dangerous. A urethral caruncle (external or inter-

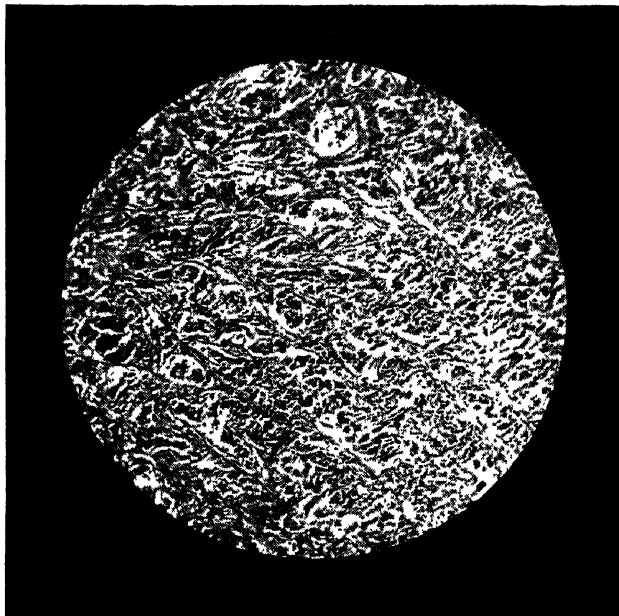


Fig. 5—Advanced carcinoma in a urethral caruncle. (Hess, E.: *Pennsylvania M. J.* 48: 1150 (Aug.) 1945.)

2. Bleeding when the lesion is touched (wiping, handling, intercourse, etc.).

3. Pain.

There may be no subjective symptoms for a long time. The lesion may be discovered accidentally by a vaginal examination or first noticed by the patient. Many pay little attention to the so-called caruncle unless the subjective symptoms become aggravated, or unless the size of the "tumor" or the bleeding is sufficient to alarm or worry them.

The so-called external caruncle is not difficult to see, nor is a mucosal eversion, but to discover the internal carun-

nal) or a mucosal eversion cannot be differentiated from a malignant lesion by any examination except that furnished by the microscope.

Forty-nine cases have been reviewed, twelve different physicians taking care of them. Only twenty-nine pathologic sections were made in the series. Fifteen cases upon which sections were made were reported as carcinoma, two as suspicious malignancies, making thirteen positive diagnoses of carcinoma out of twenty-nine sections. The clinical diagnosis of caruncle was made in fourteen cases which, under the microscope,

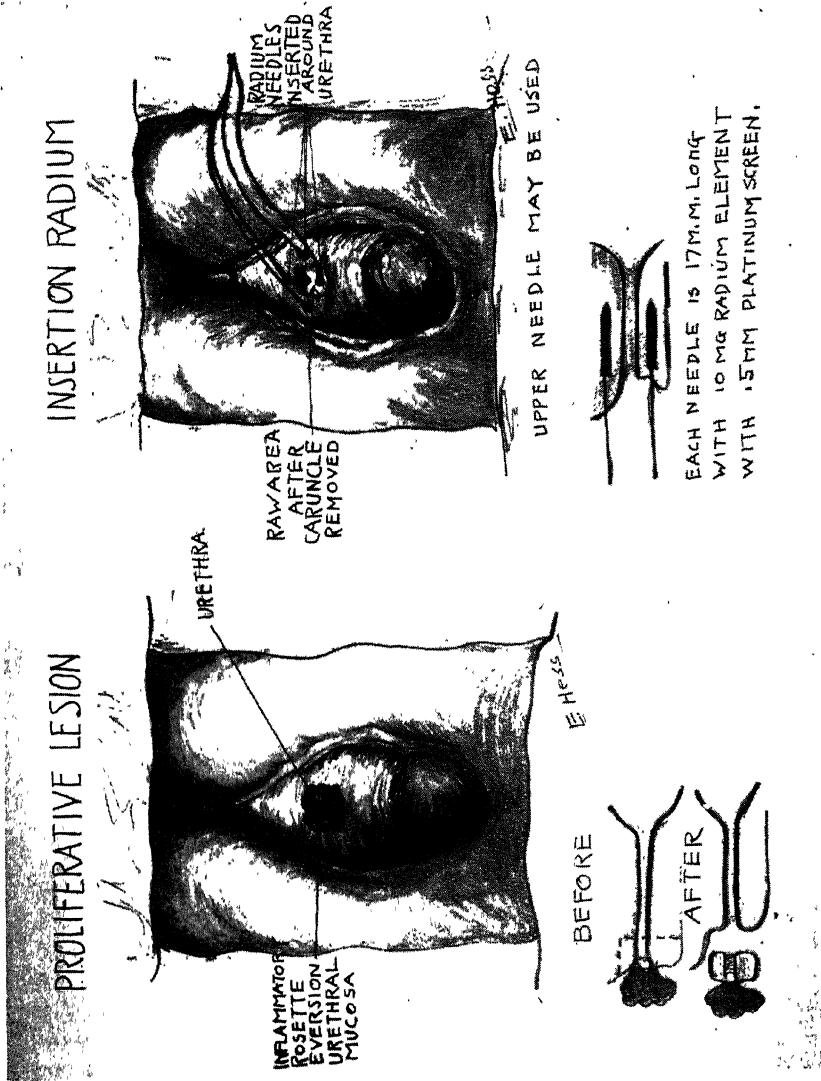


Fig. 6—Illustrates the technic of the removal of an external and an internal caruncle. (Hess, E.: Pennsylvania M. J. 48:1150 (Aug.) 1945.)

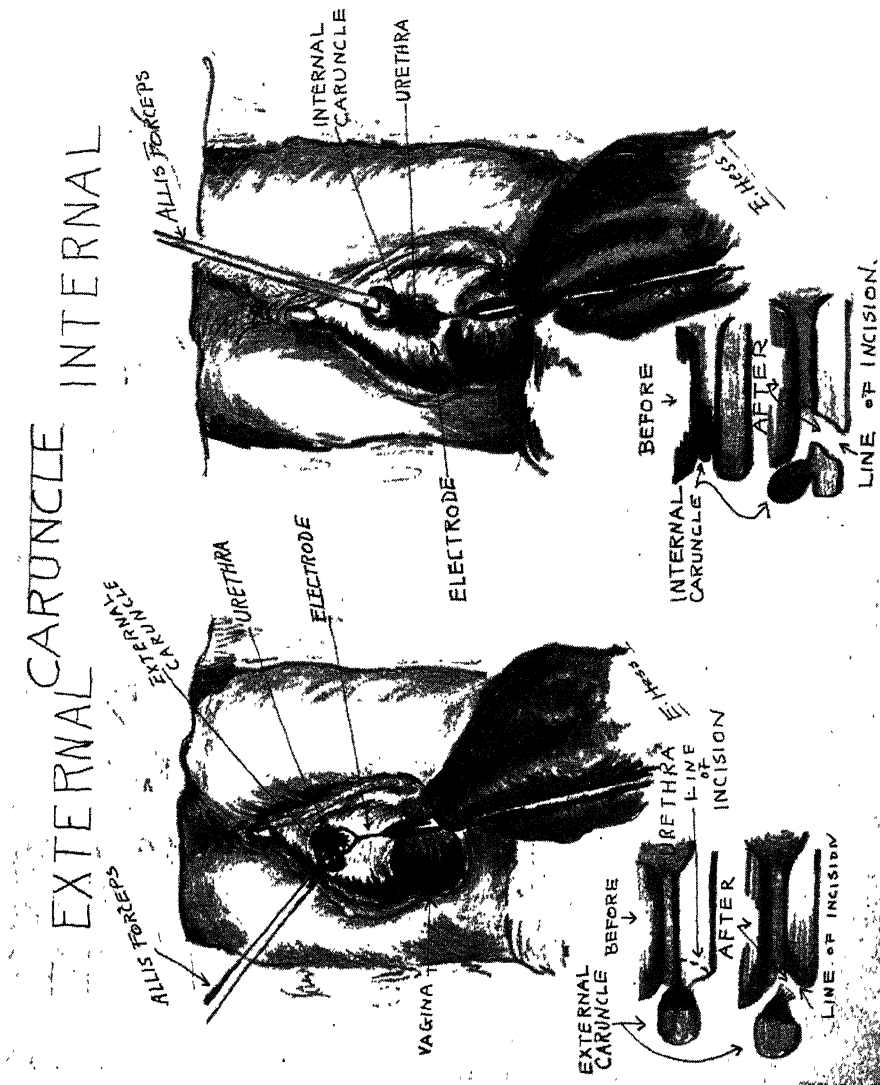


Fig. 7—Illustrates the technic of the removal of a proliferative urethral lesion and the implantation of radium. (Hess, E.: Pennsylvania M. J. 48: 1150 (Aug.) 1945.)

became definitely carcinoma. Three cases were diagnosed clinically as carcinoma and found to be simple caruncles pathologically. Only two cases were diagnosed as cancer clinically, and proven to be cancer pathologically.

The youngest patient in the series was twenty-eight, the oldest eighty-two. A study of the incidence of the condition shows that thirteen patients were between forty and fifty years old, ten between fifty and sixty years, and twenty-one between sixty and seventy years. The predominant symptom was pain in nine cases, bleeding in seven cases, frequency and urgency in only one case, and no predominant symptom was given on twenty-eight of the charts. The treatment consisted of *cauterization*, *fulguration*, and *caustic* in fifteen cases, cold dissection in five cases, and complete removal by the technic which the author employed in twenty-three cases. There is nothing in the record to show how many cases received radiation or x-ray therapy postoperatively, excepting in the author's own series, where it is used routinely. No other physician had more than one to four cases. It was noted that the gynecologist had a larger series than the general practitioner.

Fortunately, most of these cases can be cured if treated properly when first seen, whether they are benign or malignant. The management of the proven malignant case is usually *surgery* with *biopsy* and then *x-ray* or *radiation* therapy, or both. Where radium and the x-ray are used, care must be taken to keep the urethra open. This requires the use of sounds for an indefinite period of time.

The technic for the removal of these lesions is best described by the illustrations. The lesion is seized with an Allis forceps and the base is put on stretch. The electrical loop is then passed back

in the urethra so that a large piece of healthy base is removed when the current is applied. Most of the female urethra may be sacrificed with little danger of incontinence, so that even with the internal caruncles, a big bite of healthy tissue is easily obtained. The internal caruncle is best exposed by an ordinary small nasal speculum inserted in the meatus. In these two types of cases, only the floor of the urethra and a portion of the vaginal wall are sacrificed. In the type of lesion where the eversion completely surrounds the meatus, the cutting loop is pushed back above the lesion so that a cuff of urethra in healthy tissue is removed.

If the lesion proves malignant, radium needles are inserted as per the diagram. Often the needle at twelve o'clock is not considered necessary, but is often used. X-ray therapy may also be used, and if there is glandular metastasis (palpable glands in the groin should be subjected to biopsy), these glands are treated usually without good results. Unfortunately, x-ray and radium do not seem to have much effect on squamous cell carcinoma.<sup>27</sup>

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## VENEREAL DISEASES

STANFORD W. MULHOLLAND, M.D., M.S.

### Gonorrhea

The situation regarding treatment of gonorrhea has changed greatly in the past two years. In the period, 1940 to 1945, the percentage of cures reported was nearly 100 per cent and hope was expressed that gonorrhea would be completely eradicated by means of the *sulfonamide* drugs. As time goes by, it is noted the percentage of cases not responding to the sulfonamides is progressively increasing.

In the study of large groups of cases of gonorrhea in the Army during the past war, there is no doubt that sulfonamide resistance is becoming more and more common. *In vitro* experiments show some strains are normally more resistant than others, some being completely unaffected by the drug. Some strains appear to be naturally resistant while others acquire resistance, perhaps as a result of sublethal doses of the drug.

Clinically, assuming the drug is of standard potency, the explanation of sulfonamide resistance must lie either with the organism, in the patient or in the effect of one upon the other. Assuming a given strain has acquired resistance, the question arises as to whether it will remain resistant when transferred to another host. Roy<sup>1</sup> calls our attention to

the fact that in our armies in Italy, strains existed which were extremely resistant, especially when in British, American, and Canadian soldiers. Cures as low as 30 per cent were reported in these groups. He had no evidence as to whether they were resistant when in Italians or Germans.

If we assume that gonococci are either sulfonamide-resistant or sulfonamide-sensitive, it would follow that the more people treated with sulfonamides, the more likely the sensitive strains will be killed off and the relatively resistant strains survive. As time goes on, this presents a rather poor prospect for adequate control of the disease with this drug. It would follow that all the prevalent strains in a decade or so would be sulfonamide-resistant.

**Treatment with Penicillin—Dosage**—One cannot fail to note the stress made now on the early use of large doses of the drugs newly available for the treatment of gonorrhea. Where previously there was an attempt to find the minimum dose for treatment of this disease, the stress now is on adequate dosage at the onset.

It has been well established that failures in the cure have been due to inadequate dosage. It is now clinically

shown that a total dosage of 150,000 to 200,000 Oxford units gives the best percentage chances of recovery. It matters little whether the drug be given in two 100,000-unit doses over an eight- or four-hour period. Usually only the two injections will be required and results show 90 per cent cures. Patients still showing discharge at the completion of this treatment can be given smaller doses over a longer period of time, or resort can be made to one of the other methods of treatment.

It is suggested<sup>2</sup> that this more liberal use of penicillin for gonococcal infections be considered as minimizing the danger of developing penicillin-resistant strains. When penicillin was first used, it was felt the ease of application and rapidity of results would lead to inadequate follow-up on the cases and resultant re-infections and carriers developed. This probability was used as an argument against its use.

The possibility of the rapid and early treatment of gonorrhea, masking or delaying the signs and symptoms of concomitantly acquired syphilis, must always be held in mind. Ofttimes verbal warnings are not sufficient. The patients easily forget or fail to understand what is being told them. In some clinics,<sup>2</sup> pamphlets explaining the skin signs or penile lesions of syphilis are distributed to the patients at the time penicillin therapy for gonorrhea is started. Thus a visual consciousness of the seriousness of his possible neglect is brought before him.

#### ***Delayed Absorption and Secretion***

—The difficulties in adjusting penicillin treatment schedules for venereal disease patients in clinic or office practice are many. The use of normal saline as a diluent and multiple injections have not been practical for obvious reasons. Search has been made for preparations that can

be used as a single intramuscular injection, where dosage can be accurate and absorption slow to provide prolonged action of the drug. The method suggested by Romansky and Rittman<sup>3</sup> has proven valuable. The drug (penicillin, 150,000 to 200,000 Oxford units) is suspended in peanut oil, beeswax mixture or beeswax, and sesame oil mixture. The volume is kept small (2 to 5 cc.) and no complaint of pain at the site of the injection noted. There are some difficulties in handling the wax and emulsifying the penicillin, but these are overcome by experience.

The above method provides satisfactory blood levels of penicillin<sup>4</sup> for an eight-hour period and a high per cent of cures results. In a large cooperative study over the country initiated by the United States Public Health Service,<sup>5</sup> gonorrhea was reported cured in 91.2 per cent of 1060 cases by this method. The ability of this method to effect a cure does not appear to be related to sex, race, or failure of previous therapy.

Also to slow absorption, a solution of adrenalin has been incorporated in the injection of penicillin. This serves to flatten the blood level curves, rising sharply at each injection. Lesser concentrations of penicillin are found<sup>6</sup> in the samples taken right after injection and higher concentration in those taken one and one-half to three hours later. Likewise, the combination of a vasoconstrictor (neosynephrine) and colloid gelatin used with the intramuscular injection of penicillin is reported<sup>7</sup> as giving measurable levels of penicillin in the blood for as long as seven to eight hours. These results indicate only three intramuscular injections would be required to maintain a therapeutic level of penicillin in the blood for a twenty-four-hour period.

Other experiments to slow the excretion of penicillin have been done on dogs. These were done to determine whether the secretion of penicillin could be suppressed by the simultaneous administration of P-aminohippuric acid. Beyer<sup>8</sup> states there was invariably a slower rate of fall in the penicillin plasma levels after single intravenous injections of 10,000 units when P-aminohippuric acid was used. The time when the blood levels fell below detectable quantities in the blood were lengthened from two to two and one-half hours to three and one-half to four hours. The duration of time when penicillin was recoverable in the urine was increased from six and one-half to eight hours to nine and one-half to twelve and one-half hours. Whether these findings will have clinical value is a question for the future.

**Oral Penicillin**—A great amount of work has been done to find a method of administering penicillin in tablet or capsule form. It was soon found that gastric acidity destroyed the activity and limited to negligible amounts the units excreted in the urine or found in the blood. Giving penicillin on an empty stomach increased the amount found in the blood. It was noted patients with pernicious anemia (achlorhydria) would have still higher blood levels when penicillin was administered by mouth. Since that time, a host of buffers and oils have been tried to retard acidity or to pass the material into the small intestine unharmed where absorption could take place. Libby<sup>9</sup> first reported the use of sodium and calcium penicillin administered in capsules containing cottonseed oil. A single oral dose of 90,000 Oxford units maintained a satisfactory blood level (0.03 unit per 100 cc.) for four hours in the treatment of gonorrhea. Subsequent doses of 20,000 Oxford units, given three and six hours

later, maintained this blood level for seven hours.

A similar base, saponified lanolin in sesame oil, to prevent mixing of the penicillin and to protect it from the stomach acids, was suggested by Seager.<sup>10</sup> Capsules containing 10,000 to 20,000 units of penicillin in 0.5 to 1.0 gm. of the base were employed. An initial dose of 200,000 units was followed by a second dose in four to five hours. Blood levels of 0.015 unit per cubic centimeter or above were maintained over an eight-hour period. The urinary excretion varied from 3 to 20 per cent. This same base contained in an enteric-coated capsule with only 10,000-unit doses and repeated in three hours, gave blood levels ranging from 0.03 to 0.12 unit. It is apparent the enteric coating enabled satisfactory blood levels with half the original oral dosage.

The use of a suitable buffer to neutralize the gastric acidity has been tried by many. The experiences resemble those of Gryorgy,<sup>11</sup> who used penicillin in doses of 10,000 to 40,000 units every three hours in combination with trisodium citrate (1 to 5 gm. per dose). This method of administration was found to be therapeutically effective in cases of gonorrhea. The number of units necessary for administration by this method is five times that needed for parenteral therapy but are equally effective for gonorrhea.

**Rectal Administration**—In spite of the statements and findings regarding penicillinase apparently produced by the colon bacillus, Loewe<sup>12</sup> reports the use of penicillin in a suppository made with a simple coca butter base. Although no correlation between dosage and penicillin levels was reached, maximum levels up to 0.768 Oxford unit per cubic centimeter of serum were obtained with a dose of 1,000,000 units. Pro-

longed minimum levels of 0.012 unit were obtained in all dosages employed. It was concluded by this method, prolonged penicillin blood levels, sufficiently high to be effective against gonorrhea, could be obtained.

**Penicillin X**—Early in the year, there was some hope the previously discarded penicillin X might be of more value in the treatment of sulfonamide-resistant gonorrhea. Welch<sup>13</sup> reported the use of this drug in a series of sixty-eight cases where cures of 94 per cent were apparently obtained with a single intramuscular injection of 25,000 units. Blood level studies were, on a whole, somewhat higher than those in which an equal number of units of commercial penicillin were used. Likewise they reported slightly more penicillin X excreted in the urine over an eight-hour period than in the case of commercial penicillin.

**Comments**—In the use of sulfonamides for treatment of gonorrhea, it was found results were more satisfactory in the Negro. Some writers reported as many as 20 per cent more "cured" than in whites. This same relationship as to color does not hold in the case of penicillin. Likewise there seems to be no difference in regard to sex in the response to the use of penicillin. This is contrary to the opinion of some but is supported by a rather large group of cases (675) studied by Thomas.<sup>14</sup>

The salts of penicillin have been produced in a great variety to test their efficiency and relative irritation to the tissues when injected. Those salts used are sodium, lithium, ammonium, strontium, calcium, magnesium, and potassium. All seem about equally effective. Only the ammonium salt produces severe pain upon intramuscular injection in man and hemorrhagic reaction in rabbits.<sup>15</sup>

To date, there has been demonstrated some tendency for *Neisseria gonorrhea*

to develop penicillin resistance *in vitro*.<sup>16</sup> Perhaps this phenomenon may eventually occur *in vivo* and may necessitate re-evaluation of this antibiotic.

It has been found in the case of *Staphylococcus aureus* that resistance to penicillin can be stepped up to a point where 2000 times the original amount is necessary to inhibit growth. Given strains were originally inhibited by 0.04 to 0.06 unit of penicillin. When sublethal amounts were allowed in contact with the organisms, their resistance was stepped up to where they could exist when 80 to 120 units were present (Spink).

Not all workers have had the success of those flooding the present literature. As yet there has been no conclusive report concerning possible development of asymptomatic carrier states following penicillin therapy.

It would appear, for the present, that aqueous solutions of penicillin, given in two or more intramuscular injections over a period of approximately four hours or in oil beeswax suspension of penicillin given in single injections, seem to provide suitable therapy for gonorrhea. At least the present unsatisfactory response to sulfonamides justifies a change to penicillin even though it may not be the final solution to the problem of treating this disease.

One must not forget that ingenuity is necessary in the treatment of all diseases. The treatment of gonorrhea may appear to have become mechanical with the developing of new drugs. The future can only tell us whether local irrigations, artificial fever, or an individual combination of chemotherapeutic and antibiotic agents will have to be worked out for the problems that arise.

**Diagnosis of Gonorrhea**—A new note has been introduced into the accu-



racy of making diagnoses in the case of gonorrhea. A new champion for the culture method over the smear examination has been brought forth in the report of Usher<sup>17</sup> of the New Jersey State Department of Health. There has been set up a means of supplying horse plasma—hemoglobin agar slants, that are delivered by the physician to culture stations (hospitals) within three hours after streaking. He reports in 616 cases only 14 per cent of positives not detected by this method while 48.5 per cent were missed by smear examinations.

The above is directly the opposite of the confidence expressed by Riba<sup>18</sup> in smears as compared to the culture method. Riba, who was dealing only with Army personnel (males), states in his group of 450 patients cultures were helpful in only 3 per cent. Urethral smears were positive in 95 per cent of the cases. It is possible that the failure of cultures in the latter case may be due to former treatment (sulfonamide compounds) for his report was made regarding the treatment with penicillin of sulfonamide-resistant gonorrhea.

### Chancroidal Infections

The use of *sulfathiazole* in the treatment of chancroidal infections has been encouraging. However, with the use of *penicillin*, the treatment of some of the other venereal infections does not look promising. This is true in chancroidal infections and Nelson<sup>19</sup> reports the use of 1,360,000 units and 2,800,000 units in two cases of granuloma inguinale without any significant changes. The Donovan bodies were present in the tissues in one case twenty-seven days after therapy was begun.

### Lymphogranuloma

Lymphogranuloma venereum is included in some States now for which

routine diagnostic service is offered by the division of laboratories.

The complement fixation test is considered the superior method of clinching the diagnosis. In areas where this infection is found, more often the percentage of positive tests<sup>20</sup> runs about forty in the adult Negro to twelve for adult white. Children have a positive reaction when newborn, if born of infected mothers. They lose the positive characteristic in two to four months. The persistence of an immune reaction in age groups where sexual contacts are less frequent suggests the possibility the virus persists in the body, providing continued antigenic stimulus.

For making the complement fixation test, two blood specimens should be collected, one specimen to follow the other in a matter of a few days or a week.<sup>21</sup> The demonstration of the rise in complement fixation titer in the second specimen is of special significance in establishing a diagnosis in an existing lesion. A single positive test, on the other hand, may indicate either current or past infection.

### Granuloma Inguinale

Like lymphogranuloma venereum, it is thought by Anderson,<sup>22</sup> a complement fixation test will be standardized to be of distinct value in the diagnosis of granuloma inguinale.

The Donovan bodies from this latter disease have been reproduced in the epithelial cells of the yolk sac and in the yolk of a chick embryo. These micro-organisms produce in this culture antigens that elicit immune reaction in the skin and serum of granuloma inguinale patients. The complement fixation is highly specific in the serum of persons having this latter disease as compared to patients having syphilis or lymphogranuloma venereum.

It is proposed that these strains of bacterium be the type of a new genus *Donovania*, in recognition of Donovan's original description of the pathognomonic bodies of granuloma inguinale; and the specific name *granulomatis donovania* be applied to designate its relationship to the characteristic lesion of the disease.

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